The Development of Novel Gold(I)-Catalysed Reactions

Paul Christopher Young

Submitted for the degree of Doctor of Philosophy

Heriot-Watt University

Institute of Chemical Sciences,
School of Engineering and Physical Sciences

March 2014

Abstract

This thesis comprises an introduction chapter, followed by four chapters outlining the research undertaken by the author throughout the duration of study.

Chapter one gives an introduction to homogeneous gold catalysis, outlining the explosion of interest into this area of research over the past 15 years. In particular, the introduction focuses on the efforts reported in the literature involving gold(I)-catalysed reactions with cyclopropenes.

Chapter two describes the gold(I)-catalysed addition of indoles to 3,3-disubstituted cyclopropenes. The scope of the reaction is discussed, along with an investigation into the mechanism of the reaction.

Chapter three outlines the gold(I)-catalysed addition of thiols and thioacids to 3,3-disubstituted cyclopropenes. The selectivity of the reaction is discussed, as well as studies into the mechanism of the reaction.

Chapter four presents the findings into how gold(I) catalysts are deactivated in the presence of sulfur and nitrogen nucleophiles. The deactivated species formed in gold(I)-catalysed reactions are isolated and characterised, and their catalytic abilities are probed.

Chapter five describes the research undertaken into gold(I)-catalysed etherifications, utilising allylic alcohol substrates with alcohol nucleophiles. Further expansion in this area is also outlined by using novel 1,2,3-triazol-5-ylidene gold(I) catalysts, as well as the gold(I)-catalysed chroman formation from allylic alcohols and phenols.

Acknowledgements

Firstly, I would like to thank Ai-Lan for her continuous support throughout my PhD, I am extremely grateful for the opportunity to work within the Lee Group. Ai-Lan was always available when I needed to discuss any issues I encountered with my research, and her expert support and guidance was always greatly appreciated.

The Lee Group has been a fantastic team to be part of, and I would like to thank every group member (past & present) I have worked alongside for making it such an enjoyable experience. An added thank you to Graeme Barker is deserved for his kind agreement to proofread this thesis. Additionally, special thanks go to James O'Neill, Therese Bergendahl and Robert Rae for all the laughs shared throughout my PhD; their support and general banter really made the last 3.5 years fly by.

I would like to express my gratitude toward all the analytical services staff at Heriot-Watt University for their assistance throughout my PhD: Dr Alan Boyd and Dr Dave Ellis for the brilliant NMR service, Dr Georgina Rosair for XRD work and Christina Graham for CHN analysis. In addition, I would like to thank the EPSRC National Mass Spectrometry Facility for running a fast and effective service.

I would like to acknowledge the EPSRC for funding my PhD. My thanks also go to the Heriot-Watt Alumni Fund for the grant awarded to me to attend the Tetrahedron conference in Vienna, and thanks to the Royal Society of Chemistry for giving me the opportunity to present my work at the J-NOST conference in Bhopal, India.

Finally, I thank all my family and friends who have supported me throughout all my academic studies. I would especially like to thank my Mum and Dad for all their continuous support and encouragement, and thanks to David and Ruby for always keeping me on my toes.

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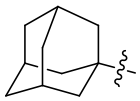
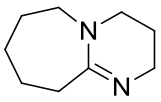
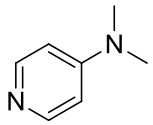
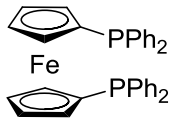
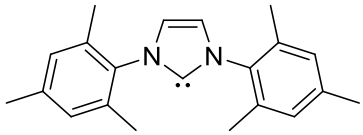
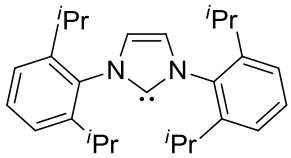
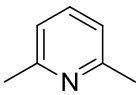
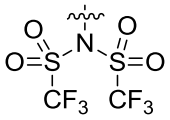
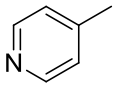
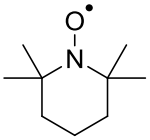
Contents

Abbreviations

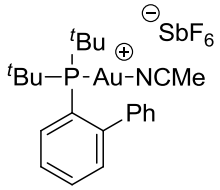
<	Less than
>	Greater than
α	Alpha
Å	Ångström (1 x 10^{-10} m)
β	Beta
δ	ppm shift
γ	Gamma
°C	Degrees Celsius
Ac	Acetyl
Ad	Adamantyl, tricyclo[3.3.1.1]decanyl 
APCI	Atmospheric pressure chemical ionisation (mass spectrometry technique)
Ar	Aryl
atm.	Atmosphere
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
^{n}Bu	Butyl
^{t}Bu	*tert*-Butyl
CI	Chemical ionisation (mass spectrometry technique)
cod	1,5-Cyclooctadiene
Cy	Cyclohexyl
DBU	1,8-Diazadicyclco[5.4.0]undec-7-ene 
DCE	1,2-Dichloroethane
DCM	Dichoromethane

DMAP	4-Dimethylaminopyridine
	
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
dppf	1,1'-*Bis*(diphenylphosphino)ferrocene
	
d.r.	Diastereomeric ratio
e.e.	Enantiomeric excess
EI	Electron ionisation (mass spectrometry technique)
equiv.	Equivalent
e.r.	Enantiomer ratio
ESI	Electrospray ionisation (mass spectrometry technique)
Et	Ethyl
g	Gram(s)
gem	Geminal
h	Hour(s)
HRMS	High resolution mass spectrometry
Hz	Hertz
IMes	1,3-*Bis*(2,4,6-trimethylphenyl)imidazol-2-ylidene
	
IPr	1,3-*Bis*(2,6-diisopropylphenyl)imidazol-2-ylidene
	
IR	Infrared
L	Ligand
LRMS	Low resolution mass spectrometry

Lut	2,6-Lutidine 
m	Meta
M	Molar (mol L^{-1})
M06	"Minnesota 06" – a density functional theory method (Y. Zhao and D. G. Truhlar, *Accounts of Chemical Research*, 2008, **41**, 157-167)
Me	Methyl
MeCN	Acetonitrile
min	Minute(s)
mg	Milligram(s)
mL	Millilitre(s)
mmol	Millimole(s)
mol	Mole(s)
MS	Molecular sieves
MW	Microwave
N/D	Not determined
NHC	*N*-Heterocyclic carbene
NMR	Nuclear magnetic resonance
NTf_2	*Bis*(trifluoromethanesulfonyl)amide 
Nu	Nucleophile
o	Ortho
OAc	Acetoxy
OTf	Trifluoromethanesulfonate (Triflate)
OTs	*p*-Toluenesulfonate (Tosylate)
p	Para
Ph	Phenyl
Pic	4-Picoline 
^{i}Pr	Isopropyl
^{n}Pr	Propyl

r.t.	Room temperature
TEMPO	2,2,6,6,-Tetramethylpiperidinyloxy 
tert	Tertiary
TFAA	Trifluoroacetic acid
TfOH	Trifluoromethanesulfonic acid (Triflic acid)
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMHQ	Trimethylhydroquinone
TMS	Trimethylsilyl, tetramethylsilane
TMTU	Tetramethylthiourea
Trz	1,2,3-triazolylidene
Ts	*p*-Toluenesulfonyl (Tosyl)
UV	Ultraviolet
Vis	Visible

Structures of Gold(I) Complexes Used in This Thesis



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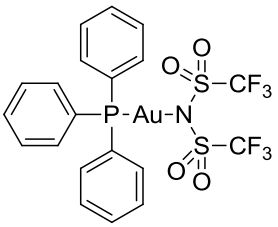

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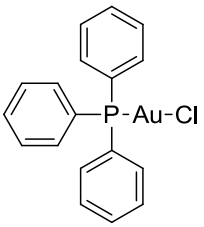
PPh_3AuNTf_2



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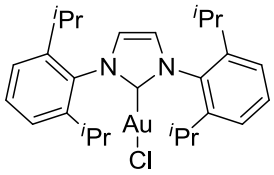

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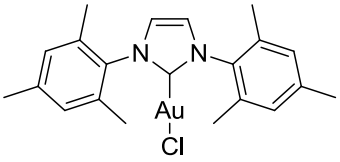
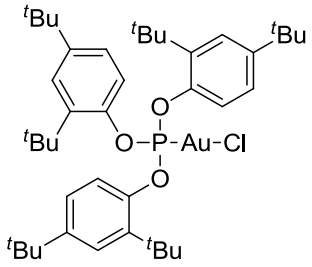
(IPr)AuCl



5
(IMes)AuCl



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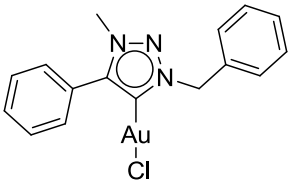

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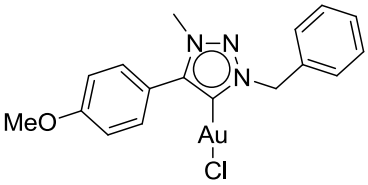

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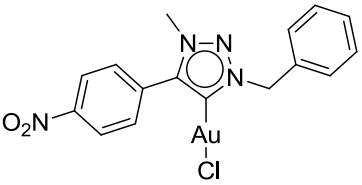

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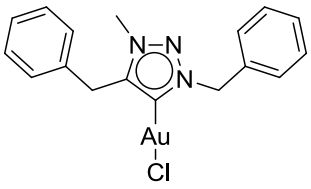

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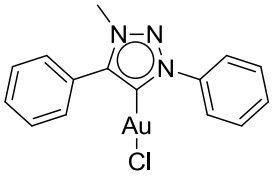

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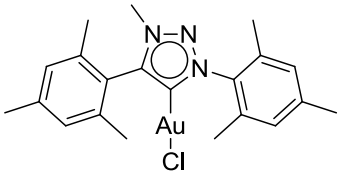

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Chapter 1 – Introduction

1.1 Gold

For centuries gold has been used in several different ways by man. As part of the noble metals in the periodic table, it is one of the few elements to be found in its inert metallic ground state form. The properties of which have led gold to become heavily used in monetary, jewellery and aesthetic applications. Originally, it was thought that because of the high stability, hence inertness, of metallic gold, it would have limited use in chemical research. However in recent times, gold was found to possess many interesting chemical properties, which has thrust it into the spotlight of popular research.[1-21]

Certain gold-containing compounds have been identified as having excellent pharmaceutical properties.[22] The orally ingested drug auranofin **13** and the injected drug sodium aurothiomalate **14** (Figure 1.1) have both been utilised to great effect for treatment of rheumatoid arthritis. There is also evidence that certain gold salts show anticancer activity, however these studies are still on-going.[22]

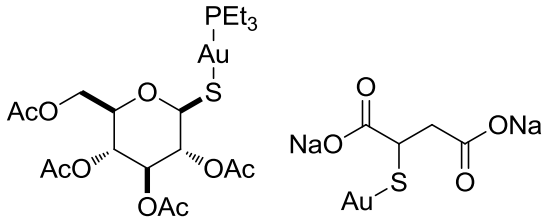


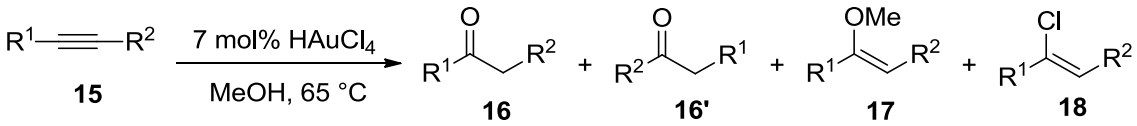
Figure 1.1. Structure of auranofin **13** and sodium aurothiomalate **14**.

Gold atoms show high electron affinity, high ionisation energies and will form strong covalent bonds. These characteristics can be attributed to relativistic effects, which are most extreme in gold atoms.[7, 23] Relativistic effects occur when electrons in the 5s orbitals penetrate the nucleus, thus experiencing strong attractive forces. As a result of these forces, the electrons will gain very high velocities, increasing their effective mass. The s-orbitals in which these electrons are travelling will contract, explaining the occurrence of the above properties.

1.1.1 Homogeneous Catalysis

Historically, gold had been relatively overlooked in terms of chemical research due to its apparent inertness and stability. The discovery of the use of gold in heterogeneous and homogeneous catalysis has led to a revolutionary change, and currently gold is at the forefront of exciting and novel research. This chapter will focus on research into homogeneous gold-catalysis, which has dramatically increased over the past decade.

One of the first reported examples of gold compounds being used in a reaction was in 1976, published by Thomas and co-workers.[24] The reaction involved gold(III) being used as an oxidant for the hydration of alkenes. A second paper was published, following this work, which appears to be the first reported instance of a gold-catalysed reaction.[25] This involved the transformation of alkynes **15** to ketones **16**/**16'**, as well as vinyl ethers **17** and vinyl chlorides **18** (Scheme 1.1).



Scheme 1.1. Gold(III)-catalysed oxidation of alkynes by Thomas.

The authors originally reported the reaction as a gold(III) oxidation, and did not fully appreciate the gold acting as a catalyst. They reported the yield of acetophenone from phenylacetylene to be 570%, calculated in reference to the amount of gold(III) used, indicating that the gold(III) was not acting as a stoichiometric oxidant but as a catalyst.

This work was also shown to be a benign, environmentally friendly alternative to stoichiometric mercury(II) hydrations, which could carry out the same transformation. The serious health and environmental issues associated with mercury are well documented, therefore utilising a catalytic metal such as gold can solve these issues.[19]

Research involving gold in homogeneous catalysis was relatively rare for several decades after these initial studies by Thomas and co-workers. However, in the 1990s there was a sudden boom in this area of research, leading to the current situation of chemistry's "gold rush".

The amount of research into gold homogeneous catalysis in the past decade bears little similarities to the amount of that back in the 1970s. The scope of transformations which are facilitated by the use of gold homogenous catalysis is increasing dramatically annually, as indicated by the sheer amount of reviews published every year.[1-21]

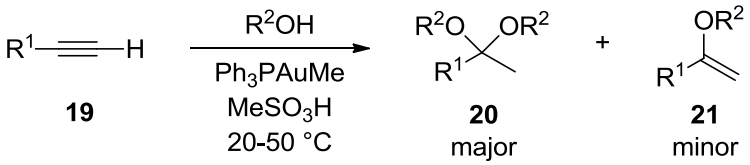
Homogeneous gold catalysts generally exist in one of two oxidation states: gold(I) or gold(III). Compounds of both oxidation states have been shown to catalyse a diverse range of reactions throughout the literature, and are known to be extremely soft and electrophilic.[26] Gold(I) catalysts tend to be very carbophilic in nature, demonstrating excellent chemoselectivity towards activation of carbon-carbon multiple bonds. This allows gold catalysis to aid the formation of new C-C, C-N, C-O and C-S bonds, through both intra- and intermolecular reactions. Although gold(III) can also activate carbon-carbon multiple bonds, catalysts in this oxidation state are generally slightly more oxophilic compared to its gold(I) counterpart. The focus of this introduction will be on the transformations utilising gold(I) homogeneous catalysis.

Gold catalysts tend to be air and moisture stable due to the high barrier of oxidation. Hence, the reactions can be carried out under extremely mild conditions, without the necessity of an inert atmosphere, which is often a practical disadvantage of other transition metal catalysed reactions. The mild conditions are also advantageous when there are potentially sensitive functional groups present in the substrates.

Perhaps the most well researched area of gold homogeneous catalysis is that with alkynes.[11] There have been numerous reactions reported in the literature which involve rearrangement or addition of nucleophiles to alkynes. These reactions have proved beneficial to industry and academia due to alkynes being commercially available at reasonable costs. Although many of the transformations of alkynes can be carried out in the presence of other metal catalysts, gold salts generally are less expensive compared to some of the more intricate platinum, rhodium or iridium complexes.[19] The gold

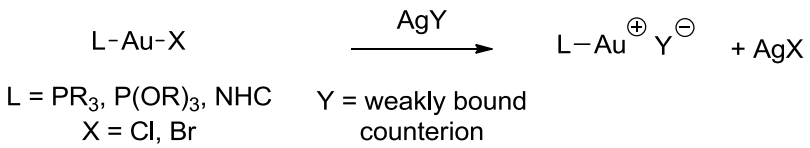
catalysts may also be regenerated from the reaction without a great deal of manipulation, making their use very appealing to industry.

A seminal paper in 1998 by Teles and co-workers was the first to describe a novel cationic gold(I)-catalyst that facilitated the highly efficient addition of alcohols to alkynes **19** (Scheme 1.2).[27] The reaction yielded acetal **20** as the major product, and vinyl ether **21** was also observed as a minor product in a number of examples.



Scheme 1.2. Gold(I)-catalysed addition of alcohols to alkynes by Teles.

The use of a strong acid (methanesulfonic acid) is required to form the active cationic gold(I) catalyst $[Ph_3PAu]^+[OMs]^-$. The presence of a strong acid in certain reactions is not viable due to potential acid-sensitive functional groups. However, over the years new methodologies have been developed to avoid the use of these strong acids in gold(I)-catalysed reactions. One of the current favoured methods is addition of a silver co-catalyst (such as AgOTs, $AgSbF_6$ *etc*.) to an inactive parent gold species L-Au-X (where L = ligand and X = Cl or Br), thereby forming the active cationic gold(I) catalyst *in situ* (Scheme 1.3). Alternatively, there have been efforts made into synthesising discrete cationic gold(I) complexes, which are stable and ready to use without addition of a co-catalyst. Examples of these types of complexes are the commercially available species **1**[28] and **2**,[29] designed by Echavarren and Gagosz respectively (Figure 1.2).



Scheme 1.3. Formation of active cationic gold(I) species *in situ*.

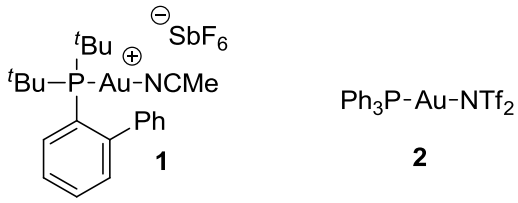
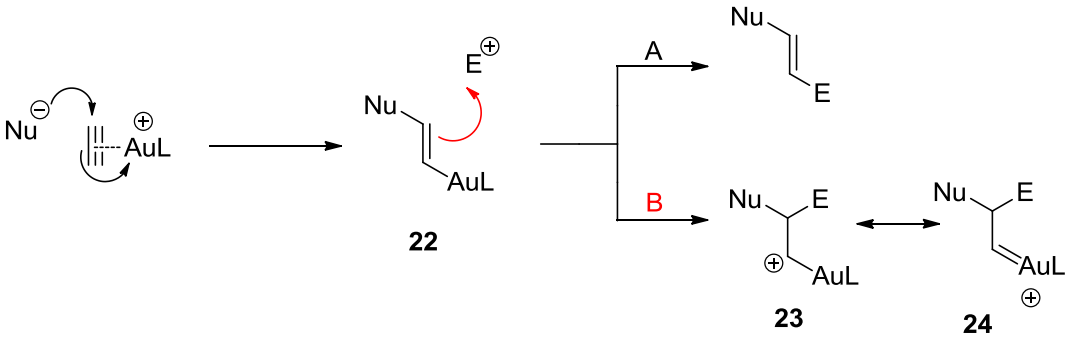


Figure 1.2. Echavarren's and Gagosz's air stable cationic gold(I) catalysts.

1.1.2 Bonding and Mechanisms

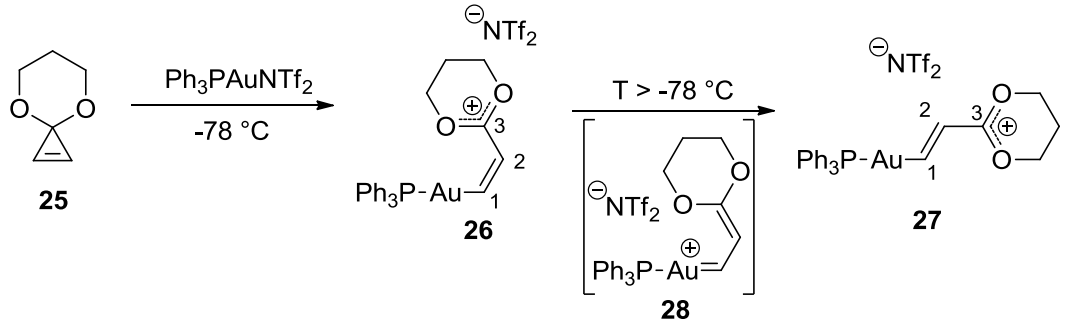
The intermediates formed in gold(I)-catalysed reactions have been the subject of much debate and interest, and currently isolating and characterising these species is a hot topic of research (for a further discussion into isolation and characterisation of these intermediates, see Chapter 4). Initial efforts into the bonding and mechanisms of these reactions focused on whether the gold-carbon intermediates were more characteristic of a gold-carbene **24** or a gold-stabilised carbocation **23** (Scheme 1.4).[7, 30-32]



Scheme 1.4. Proposed gold-carbene/carbocation intermediates.[7]

Gold(I) catalysts selectively activate alkyne carbon-carbon unsaturated bonds toward nucleophilic attack, resulting in vinyl-gold species **22**. Protodemetallation of species **22** can occur, to access a multitude of reported products (route A, E = H^+). Alternatively, it could be envisaged that gold could help stabilise an α-carbocation **23**, leading to a potential gold-carbene **24** (route B). Work carried out by Fürstner[32] and Toste[7, 31] provide arguments for the formation of a carbocation and a gold-carbene respectively.

An NMR study by Fürstner and co-workers provided experimental evidence of the cationic nature of the gold-carbon intermediate (Scheme 1.5).[32] Cyclopropene **25** was found to undergo ring-opening on addition of a gold(I) catalyst at low temperatures, affording vinyl-gold species **26** (see section 1.3 for further explanation on the gold(I)-catalysed ring opening of cyclopropenes). The species **26** will rearrange from the *Z*-isomer to the *E*-isomer **27** when the temperature is increased above -78 °C.



Scheme 1.5. Fürstner's experimental evidence of a carbocation species.

The authors monitored the ^{1}H NMR spectra of **26** and only one signal was observed for the proton on C2, which the authors suggest demonstrates that there is rapid rotation about the C2-C3 bond, even as low as −78 °C. This observation is consistent with the proposed carbocation **26**, and not the gold-carbene species **28**.

At higher temperatures (> −78 °C), a mixture of both *Z*- and *E*-isomers were present in the ^{1}H NMR spectrum, however there is no significant line broadening. This observation suggested that there is no major exchange between these two isomers occurring, and therefore the barrier to interconversion must be high. A high barrier to interconversion (along with the characteristic *J*-coupling patterns) implied that the C1-C2 bond showed double bond character, and not the C2-C3 bond, once again providing further evidence of the presence of carbocation species **26**.

The authors conclude that the evidence gathered from the NMR study provides evidence for the formation of species that are cationic in nature. However, the cyclopropene substrate **25** used throughout the study contains two oxygen substituents attached to C3, which raises the question of how much input these electron-rich substituents have on the overall stabilisation of carbocation **26**. A follow up report by Toste demonstrates just how significant the substituents are to the stabilisation of the gold-carbon intermediates.[31]

Toste and co-workers initially calculated the activation energies of rotational barriers, since this gives an indication of the strength of π-bonds. (Figure 1.3). The calculated energies were in good agreement with the experimental values, and therefore backed up Fürstner's claims that the gold has a negligible effect on the rotational barrier. For example, the bond rotation for species **26** was calculated to be 10.6 kcal mol^{-1}, which was in excellent agreement with the experimental value of 11.0 kcal mol^{-1}.

However, the authors state that this is only true in situations where there are stabilising oxygen substituents. When these oxygen atoms are removed from the structures, the calculated bond rotation energies significantly change. Species **30** does not have a vastly different bond rotation energy compared to its analogous gold-species **26** (9.2 *vs.* 11.0 kcal mol^{-1}). If the oxygen substituents are removed from the substrate, the bond rotation increases to 14.4 kcal mol^{-1} for species **31**. Reintroducing a gold moiety to the structure **33**, further increases the bond rotation energy to 22.5 kcal mol^{-1}. The conclusions drawn from this study was that the substituents on each substrate play a major role in determining the overall carbene/carbocation nature of the intermediates.

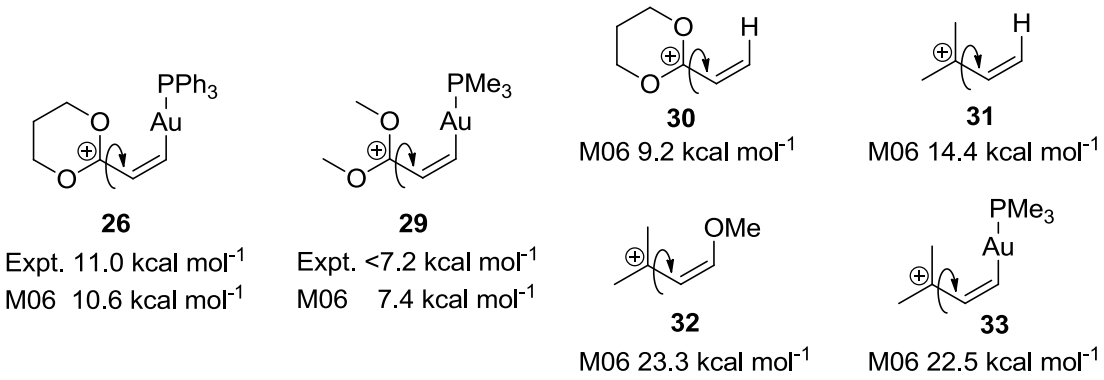


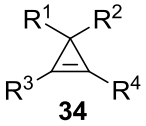
Figure 1.3. Calculated and experimental energies of bond rotation.

The authors state that the ligand on the gold also plays a major role in determining the extent of cationic/carbene nature of the species. Ligands which are more π-acidic (e.g. phosphite ligands) are more likely to promote carbocation-like reactivity due to a decrease in back-donation from the gold to the carbon substituent. Those ligands which promote back-donation from the metal centre to the carbon substituent, and therefore decrease σ-donation from the carbon to the gold centre (e.g. NHC-ligands), show more carbene-type behaviour.

Toste and co-workers conclude their findings by suggesting that the intermediates should be viewed as sitting on a continuum, ranging from a gold-coordinated carbocation to a gold-stabilised singlet carbene. The true nature of the species is dependent on both the substituents on the carbene substrate, and the ligand attached to the gold centre.

1.2 Cyclopropenes

Cyclopropenes **34** are highly strained, three-membered ring molecules (Figure 1.4). The high strain of the ring results in cyclopropenes being highly reactive, thus leading to interest from many research groups to study their behaviour in different reactions. Research into the reactivity of cyclopropenes is becoming increasingly popular, perhaps due to the many accessible products from different reactions. Cyclopropenes can also be found in some naturally occurring substances, such as cottonseed oil.[33]

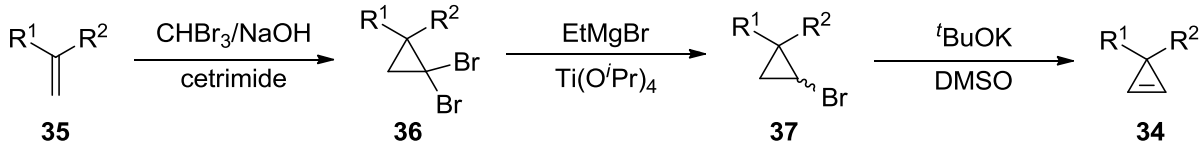


34

Figure 1.4. General cyclopropene skeleton.

There are currently two popular methods of synthesising 3,3-disubstituted cyclopropenes on large scale, both are outlined by Gevorgyan.[34] 3,3-Disubstituted cyclopropenes have the advantage of providing information into a reaction's facial selectivity (whether it is sterically controlled or directing-effects). This benefit, along with having a considerable shelf live and being easy to handle, make 3,3-disubstituted cyclopropenes very desirable as building blocks in organic synthesis.

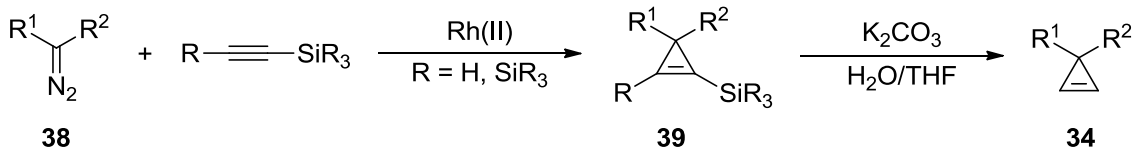
The first method discussed by Gevorgyan is a three-step synthesis of 3,3-disubstituted cyclopropenes (Scheme 1.6). Starting from an alkene **35**, a dibromocarbene addition is performed; affording a dibromocyclopropane **36**. This is followed by a reduction to give the corresponding monobromocyclopropane **37**.[35] To obtain the desired cyclopropene **34**, a debromination elimination reaction is required.



35 **36** **37** **34**

Scheme 1.6. General method for large scale synthesis of 3,3-disubstituted cyclopropenes.

The second method (Scheme 1.7) uses a diazo starting material **38**. The diazo compound undergoes metal-catalysed decomposition and then reacts with the silylalkyne. The resulting silylcyclopropene **39** can then be deprotected, giving the desired cyclopropene **34**. Both synthetic routes achieve high yields and are relatively inexpensive to carry out.

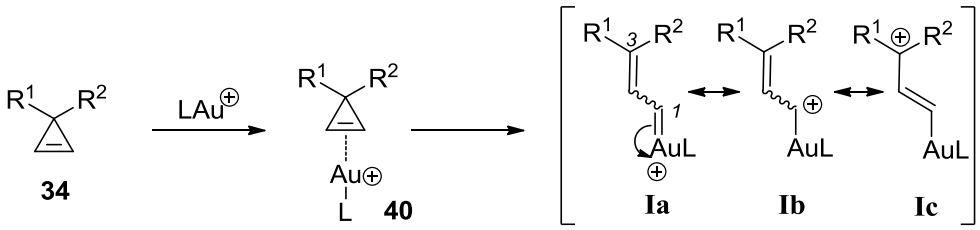


38 **39** **34**

Scheme 1.7. General method for large scale synthesis of cyclopropenes from diazo compounds.

1.3 Gold(I)-catalysed reactions with cyclopropenes

The high ring strain of cyclopropenes result in their potentially high reactivity. Transition metals have previously been reported to activate cyclopropenes; both rhodium(II)[36] and palladium(II)[37] have resulted in rearrangements of cyclopropenes. However, gold(I) catalysts has only recently been utilised with cyclopropenes. It was found that cyclopropenes **34** are activated by gold(I) catalysts, and will undergo ring-opening (Scheme 1.8). The resulting intermediate, which can be represented as mesomeric intermediates **Ia-c**, is then able to react *via* a variety of pathways, resulting in a diverse range of novel reactions being reported in the literature.



Scheme 1.8. Gold(I)-catalysed ring-opening of cyclopropenes.

In order to shed light upon the exact mechanism of the gold(I)-catalysed ring-opening of cyclopropenes, computational studies have been carried out.[38, 39] Lee and Macgregor reported their findings on a $[(PPh_3)Au(c\text{-}C_3H_4)]^+$ **41** model system (Figure 1.5).[38] Initially, the gold(I) moiety binds in a symmetrical fashion with Au-C1 and Au-C2 bond lengths of 2.26 Å, and a C1-C2 bond length of 1.36 Å (0.05 Å longer than the free cyclopropene). The calculated transition state structure **[42]**‡ demonstrates a slippage of the gold(I) moiety from the centre of the alkene bond, towards C1. The Au-C1 shortens to 2.13 Å, and the Au···C2 distance has dramatically increased to 3.08 Å, suggesting that a formal bond is no longer present. The C1-C3 bond also increases from 1.52 Å in **41** to an elongated bond of 1.62 Å in **[42]**‡. The ring-opened intermediate **43** shows a further decreased Au-C1 bond of 2.00 Å, while the Au-C2 interaction and the C1-C3 bond are completely broken. The model system studied showed that the gold(I)-catalysed ring-opening of the cyclopropene is kinetically accessible ($\Delta E^‡$ = 6.6 kcal mol^{-1}), and exothermic (ΔE = 10.5 kcal mol^{-1}).

The gold(I)-facilitated ring-opening of cyclopropenes has led to a growing number of novel reactions being reported in the literature. Both intramolecular and intermolecular examples have been reported, accessing a wide range of useful products.

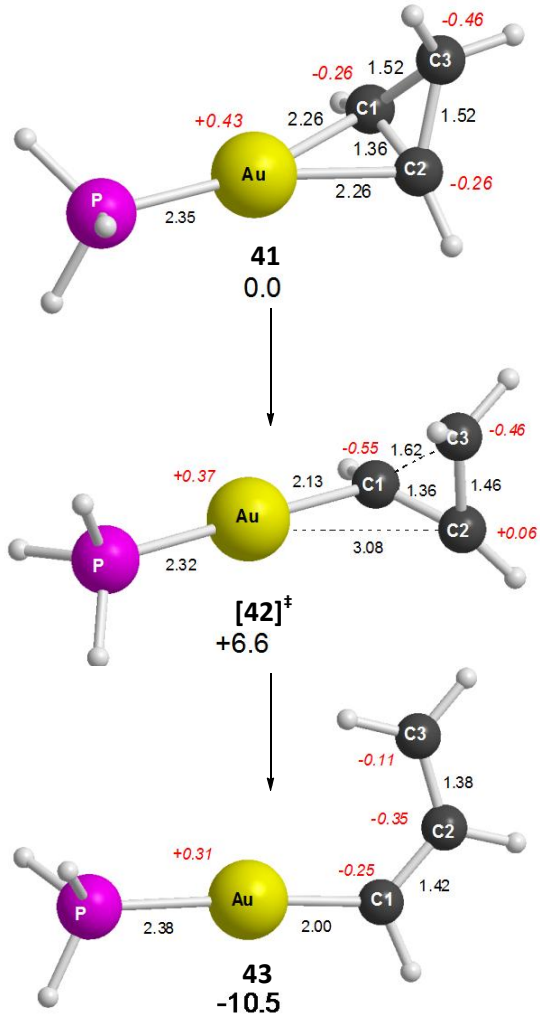
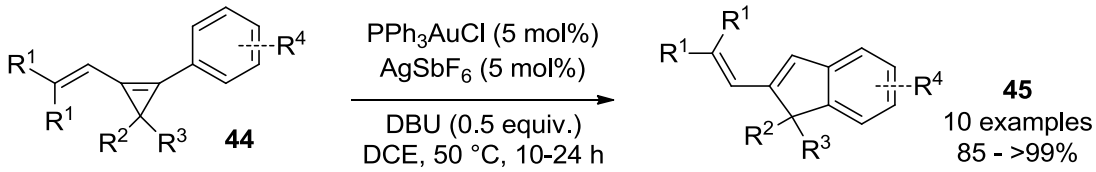


Figure 1.5. Computed structures for the ring opening of cyclopropene. Selected distances (Å) are shown in plain text and computed natural charges in italics. Relative energies are in kcal mol^{-1}.

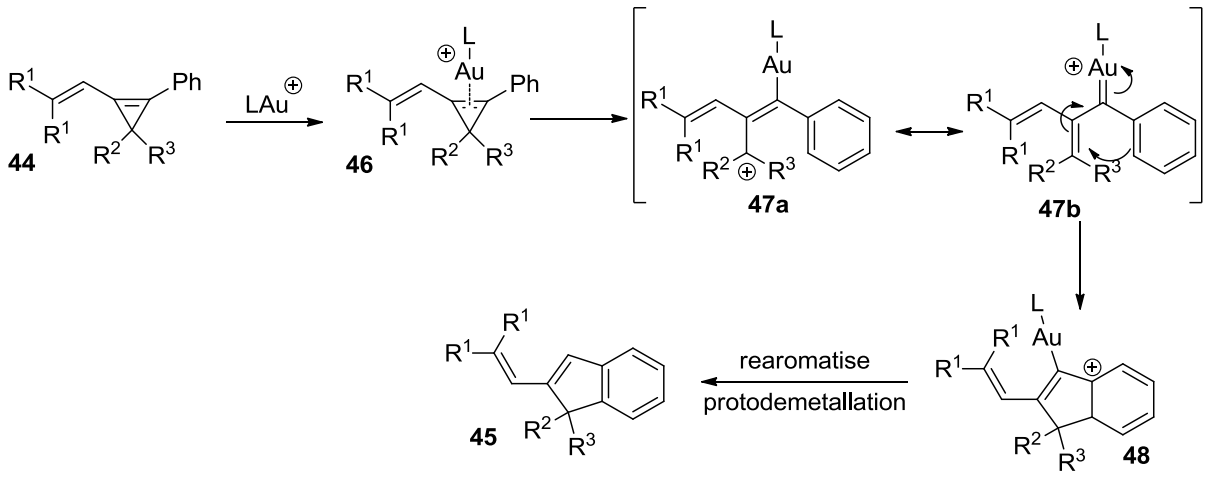
1.3.1 Intramolecular Reactions

The first reported intramolecular gold(I)-catalysed reaction with cyclopropenes was by Shi and co-workers.[40] The formation of indene skeletons **45** was achieved by the gold(I)-catalysed cycloisomerisation of arylvinylcyclopropenes **44** (Scheme 1.9). A wide range of substituents were investigated, each resulting in high yields of products. However, it was noted that with electron-deficient substituents on substrate **44**, the reaction required the use of the less coordinating SbF_6^- anion from the silver salt. If a more coordinating counterion was utilised, only trace amounts of product were obtained.



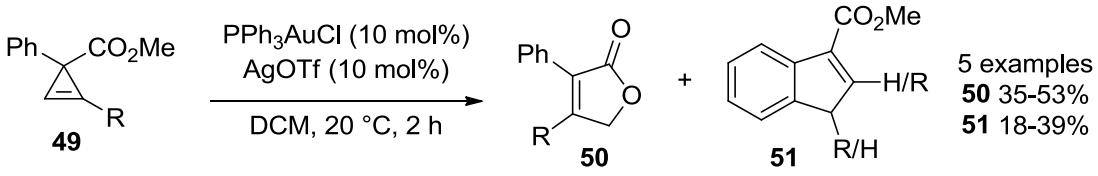
Scheme 1.9. Gold(I)-catalysed cycloisomerisation of arylvinylcyclopropenes by Shi.

The authors suggest that the mechanism begins with the gold(I)-activation of the cyclopropene alkene bond **46** (Scheme 1.10). Ring-opening can then occur, leading to the resonance intermediates **47a** and **47b**. An intramolecular conjugate addition reaction on **47b** (or Friedel-Crafts-type reaction on **47a**) can then occur, leading to the cycloisomerised intermediate **48**. The desired product **45** is released after rearomatisation and protodemetallation.

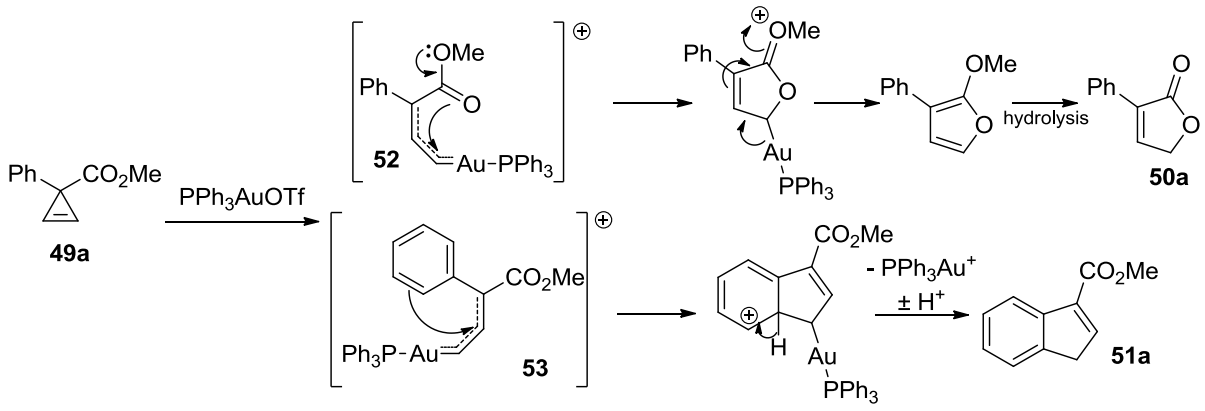


Scheme 1.10. Proposed mechanism of gold(I)-catalysed rearrangements of arylvinylcyclopropenes.

In a paper published around the same time as Shi's gold(I)-catalysed cycloisomerisation work, the Lee Group reported their findings on the gold(I)-catalysed intramolecular rearrangements of 3,3-disubstituted cyclopropenes with carbonyl and phenyl substituents **49** (Scheme 1.11).[41] The proposed mechanism is shown in Scheme 1.12, which accounts for the formation of both products. The major product in the reaction was found to be butenolide **50**, resulting from the intramolecular attack of the carbonyl oxygen from the ester functionality (intermediate **52**). The indene minor product **51** is obtained through intramolecular attack from the phenyl substituent (intermediate **53**).



Scheme 1.11. Gold(I)-catalysed rearrangement of cyclopropenes by Lee.



Scheme 1.12. Proposed mechanism for the gold(I)-catalysed rearrangement of cyclopropenes.

A computational study was carried out by Lee & Macgregor to further elaborate on this gold(I)-catalysed rearrangement, in order to explain the selectivities and ratios of products **50** and **51**.[38] The computational results confirmed that the proposed mechanism (Scheme 1.12) is valid. Two separate pathways were found to exist to account for the formation of each product (Figure 1.6). The bottom reaction profile (in black) shows the formation of butenolide **50a** (where R = H). Interestingly, the process begins with the gold(I) catalyst coordinated to the carbonyl oxygen **54**, and *not* coordinated to the cyclopropene alkene bond. The reaction proceeds through a transition state **55** at +12.0 kcal mol^{-1}, resulting in intermediate **56** at −13.2 kcal mol^{-1}. This

species **56** is orientated correctly (with the carbonyl group *cis* to the gold(I) moiety) to allow nucleophilic attack by the carbonyl oxygen on to the C1 position, and hence setting up the skeleton of the butenolide product. This proceeds with an energy barrier of 5.9 kcal mol^{-1}, resulting in transition state **57**, which progresses to give the stable intermediate **58** at −35.7 kcal mol^{-1}. Protodemetallation and hydrolysis must then occur to release the final butenolide **50a**.

An alternative pathway was found to account for the formation of indene **51a**. The top reaction profile (Figure 1.6, in blue) explains the differences in reaction intermediates that lead to the formation of the indene product. Initially, the gold(I) catalyst binds symmetrically to the cyclopropene **59**, which in comparison to the *O*-bound gold species **54**, has an energy of 5 kcal mol^{-1} higher. The reaction proceeds through transition state **60** with a barrier of 10 kcal mol^{-1}, resulting in intermediate **61** at −10.6 kcal mol^{-1}. In contrast to the butenolide **50a** formation, the phenyl ring is now *cis* to the gold(I) moiety, which overcomes a reaction barrier of 5.2 kcal mol^{-1} to allow attack from the phenyl ring on to the C1 position **62**, setting up the indene product skeleton. This transition state then progresses to the stable intermediate **63** at −26.0 kcal mol^{-1}. Indene **51a** is released following rearomatisation and protodemetallation of the gold(I)-species.

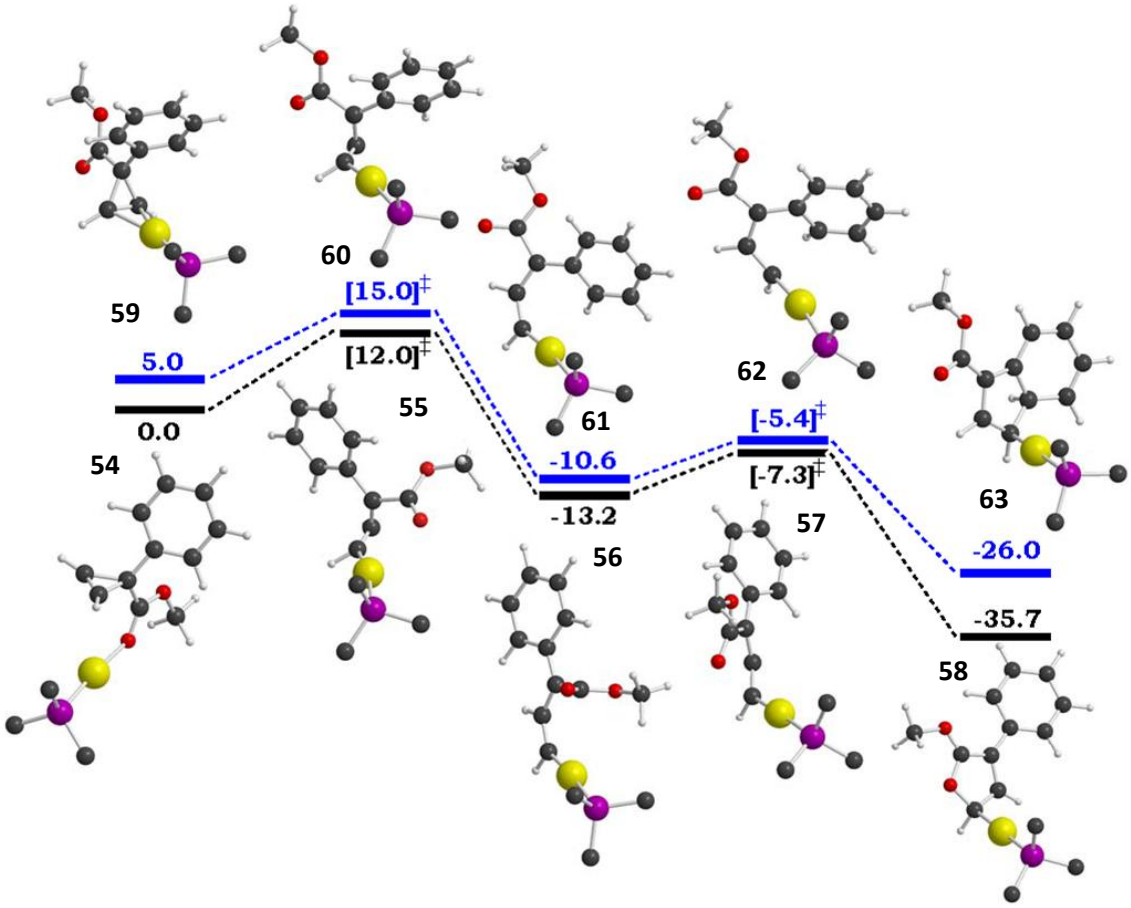
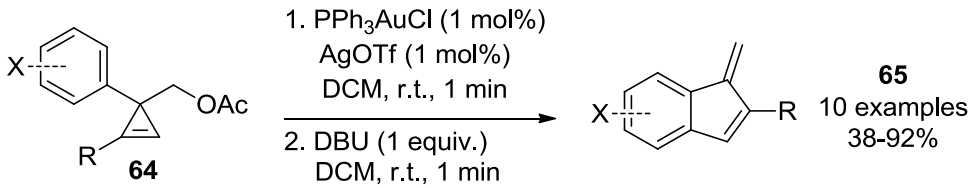


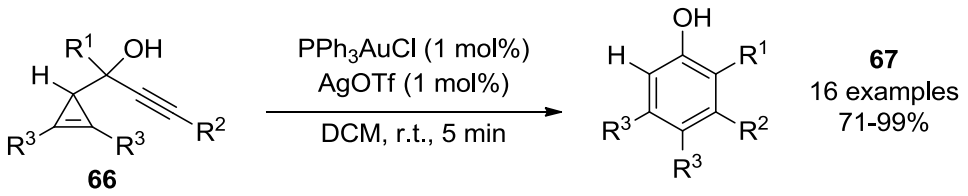
Figure 1.6. Computed partial reaction pathway for the formation of **50a** and **51a** (values in kcal mol^{-1}).

A related intramolecular isomerisation reaction was reported by Wang and co-workers in 2009.[42] Cyclopropenes of type **64** were found to undergo intramolecular cycloisomerisation and elimination of acetic acid in a one-pot fasion, affording indene products **65** (Scheme 1.13). The first step involves the cycloisomerisation of the cyclopropene, *via* attack from the phenyl substituent (mechanism follows that suggested by Lee & Macgregor).[38] The final product **65** is obtained from the base-induced elimination of acetic acid by DBU. Since this reaction is extremely fast and mild (with excellent functional group tolerance), the authors argue that this is a more efficient procedure to utilise compared to the analogous rhodium(II)-catalysed transformation which requires higher temperatures (60 °C) and longer reaction times (48 h).[43]



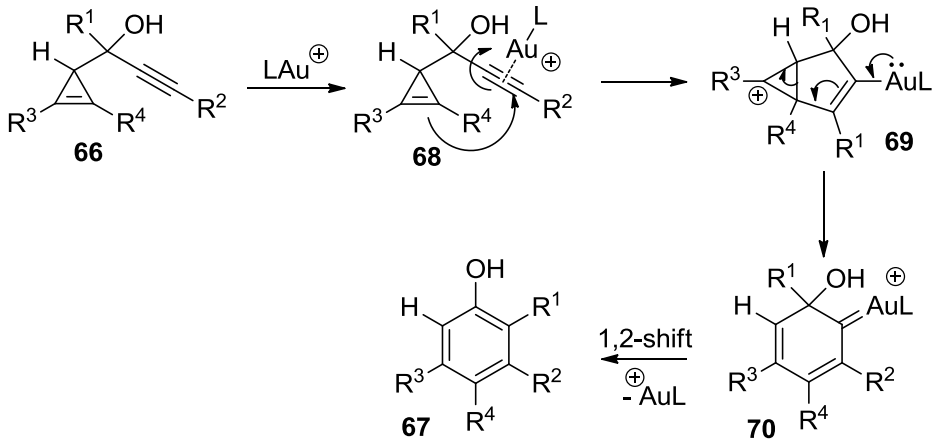
Scheme 1.13. Gold(I)-catalysed isomerisation of cyclopropenes by Wang.

The following year in 2010, Wang and co-workers reported their findings on the gold(I)-catalysed formation of phenol derivatives (Scheme 1.14). In the presence of a gold(I) catalyst, propargyl cyclopropenes **66** will undergo cycloisomerisation to afford benzene derivatives **67**. The mild reaction conditions, once again, render it very tolerant toward various functional groups (including esters and amines). It is noteworthy to mention that the alcohol functionality in the substrate **66** is not required, as shown by the rearrangement of a substrate with the alcohol group replaced with a proton (resulting in 97% of the corresponding benzene derivative product).



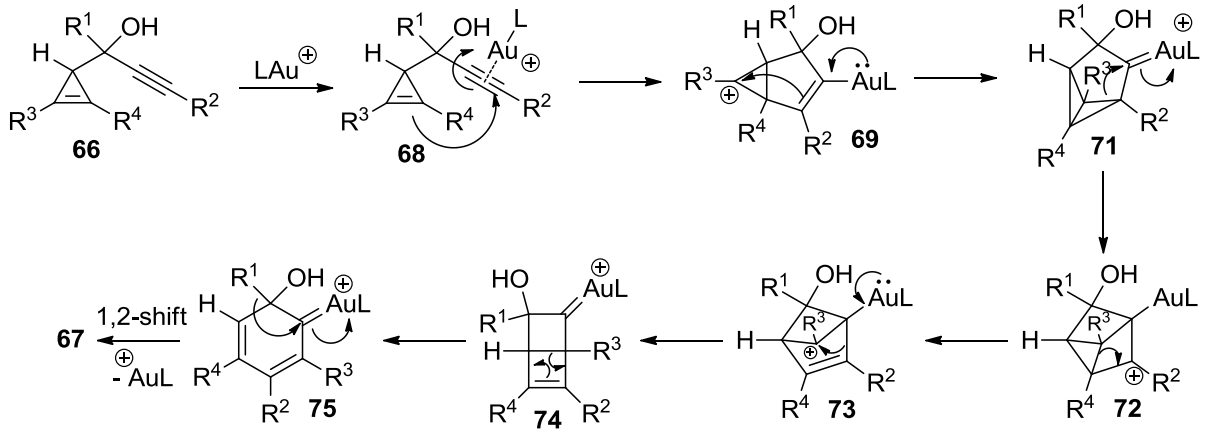
Scheme 1.14. Wang's gold(I)-catalysed cycloisomerisation of propargyl cyclopropenes.

The authors state that there are two possible mechanistic pathways to achieve the product **67**. The first proposed mechanism is outlined in Scheme 1.15, and involves no skeletal rearrangement of the unsaturated bonds. The mechanism initiates with activation of the alkyne by the gold(I) catalyst **68**, subsequently followed by nucleophilic attack (5-*endo-dig*) by the cyclopropene alkene moiety, affording the bicyclic cation **69**. This species undergoes ring-opening, giving species **70**, which liberates the desired product **67** following a 1,2-shift of the R^1 substituent and rearomatisation *via* loss of LAu^+.



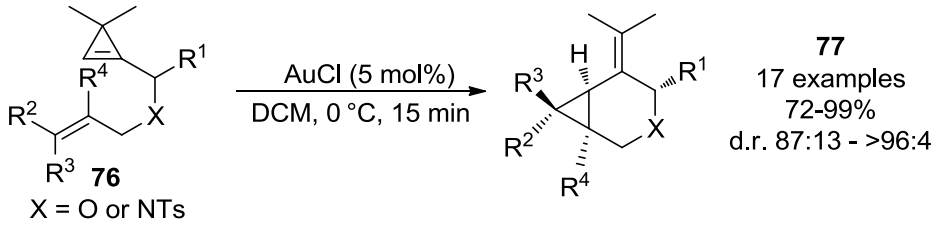
Scheme 1.15. Proposed non-skeletal rearrangement mechanism.

The second proposed mechanism involves complete cleavage of both the cyclopropene alkene bond, and the alkyne bond (Scheme 1.16). The initial steps of the mechanism follows the same pathway as that outlined in Scheme 1.15, affording species **69**. Three consecutive 1,2-alkyl shifts can then occur, completely cleaving the double and triple bonds, resulting in Dewar-type benzene species **74**. Ring-opening of this species, followed by a 1,2-shift of substituent R^1 releases the desired product **67**. This double cleavage mechanism could account for the regioisomers observed when using specific substrates.



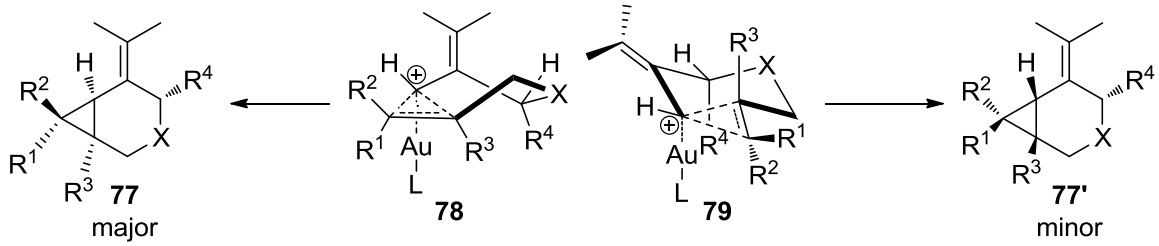
Scheme 1.16. Proposed mechanism with double cleavage process for cycloisomerisation.

Cossy and Meyer have outlined the efficient formation of 3-oxa- and 3-azabicyclo[4.1.0]heptanes **77** facilitated by a gold(I)-catalysed reaction (Scheme 1.17).[44, 45] The reaction involves using an allyl 3,3-dimethylcyclopropenylcarbinyl ether or sulfonamide **76**, which readily undergoes a gold(I)-catalysed cycloisomerisation yielding products of the type **77** in impressive yields and high diastereoselectivities.



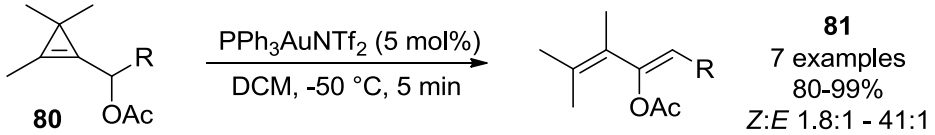
Scheme 1.17. Gold(I)-catalysed cycloisomerisation of cyclopropene-enes.

The excellent level of diastereoselectivity was attributed to the transition state of the reaction.[45] The presence of the *gem*-dimethyl group in the molecule determines the position of the substituents. It is evident from the proposed stereochemical rationalisation (Scheme 1.18) that a twist boat conformation **78** would be preferred over the chair-like transition state **79**. To minimise 1,3-strain with the gold(I) moiety, the R^4 group is forced into a *pseudo*-axial position, leading to the observed major product **77**. The chair-like transition state **79** requires the gold(I) and R^4 to be in axial positions, resulting in severe 1,3-strain and thus rendering the product **77'** the minor isomer.



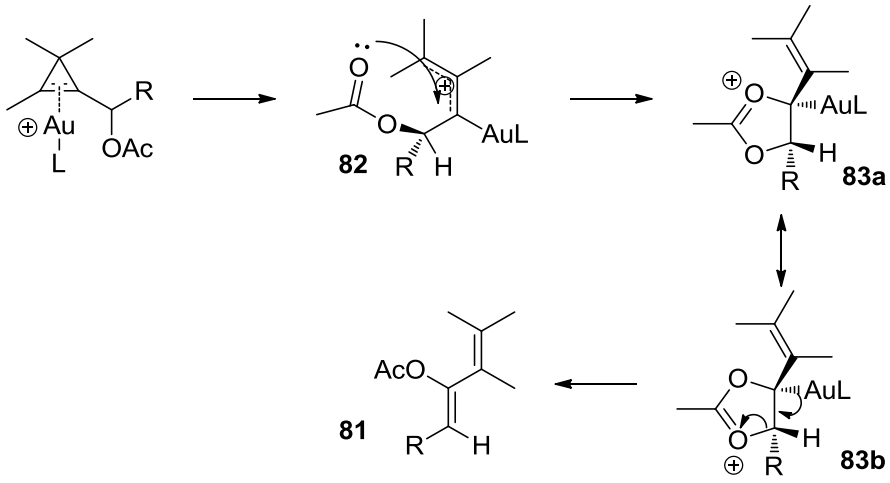
Scheme 1.18. Proposed stereochemical outcome rationalisation by Meyer and Cossy.

A study by Hyland and co-workers demonstrated how cyclopropenylmethyl acetates **80** behave when subjected to gold(I) catalysis conditions (Scheme 1.19).[46] The cyclopropene substrates **80** were found to undergo rearrangement to selectively yield *Z*-acetoxydienes **81**. The lower temperature is necessary to retain the *Z*-selectivity of the reaction; carrying out the reaction at higher temperatures resulted in an increase of the *E*-isomer being formed.



Scheme 1.19. Gold(I)-catalysed diene formation from cyclopropenes by Hyland.

The authors also provided a proposed mechanism of diene formation (Scheme 1.20), computational analysis was carried out to determine the theoretically favoured reaction pathway. It was concluded that the ring-opening pathway suggested by Lee and co-workers was kinetically favoured.[41] After the gold(I)-facilitated ring-opening of the cyclopropene, nucleophilic attack from the carbonyl oxygen can occur (**82**). An overall 1,2-migration of the acetoxy group occurs *via* the five-membered intermediates **83a**/**83b**, to release the observed product **81**. The computational calculations determined that the formation of the *Z*-isomer proceeds with a lower energy barrier, due to reduced steric interactions compared to the *E*-isomer formation.

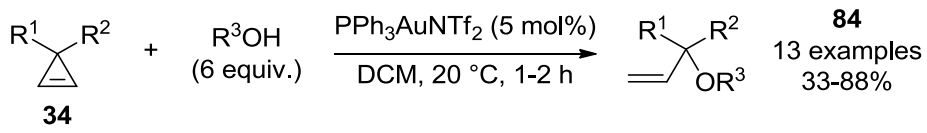


Scheme 1.20. Proposed mechanism for the gold(I)-catalysed diene formation.

The field of intramolecular gold(I)-catalysed reactions with cyclopropenes has been well developed, with a number of interesting rearrangements observed by several research groups. However, for these rearrangements to take place, the substrates must have all the functionalities required previously installed through usually lengthy sequences. Therefore it was highly desirable to also achieve *intermolecular* transformations, in order to add various functional groups to the cyclopropene substrates.

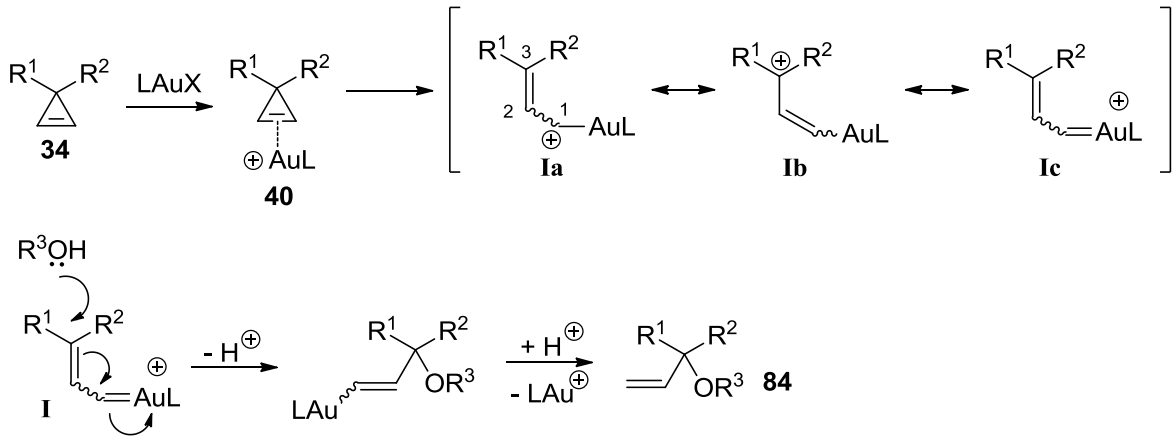
1.3.2 Intermolecular Reactions

The first intermolecular gold(I)-catalysed reaction with cyclopropenes was reported by the Lee Group in 2008.[41, 47] Alcohols were found to act as an effective nucleophile with cyclopropenes **34**, under gold(I)-catalysed conditions, resulting in the regioselective formation of tertiary allylic ethers **84** (Scheme 1.21).



Scheme 1.21. Gold(I)-catalysed addition of alcohols to cyclopropenes.

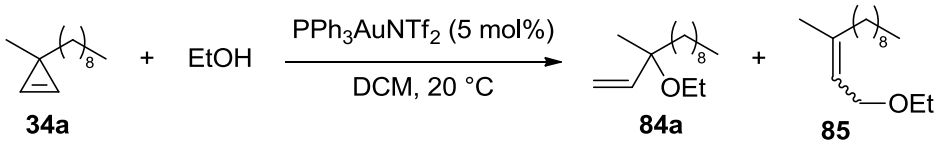
The excess alcohol is necessary in order to suppress the formation of the *primary* allylic ether isomer, as both the primary and tertiary allylic ethers can be formed (Scheme 1.22). The gold(I) catalyst activates the cyclopropene alkene bond, resulting in ring-opening to give intermediate **I** (represented as three possible resonance structures **Ia-c**).[38] Nucleophilic attack by an alcohol can occur at the C1 or C3 position, leading to potential mixtures of the primary allylic ether or tertiary allylic ether respectively. However, through the reaction optimisation process, it was found that the use of excess alcohol regioselectively produces the *tert*-allylic ether **84** (*i.e.* alcohol attack at the C3 position).



Scheme 1.22. Proposed mechanism of gold(I)-facilitated formation of *tert*-allylic ethers.

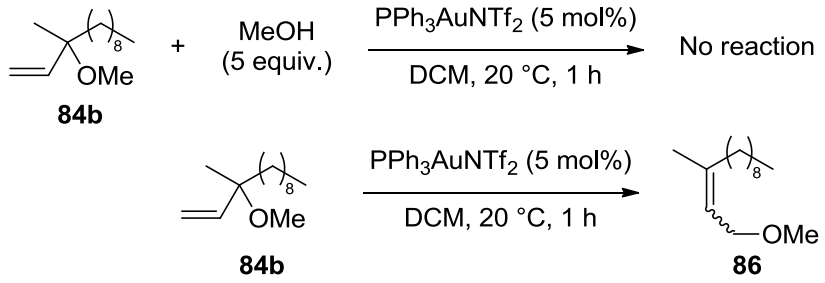
Indeed, when the authors attempted a reaction with the alcohol not in excess, a severe reduction in regioselectivity was observed (Table 1.1). The use of 6 equivalents and 3 equivalents of nucleophile alcohol produced the corresponding *tert*-allylic ether **84a** with a regioselectivity of >99:1 (entries 1-2). Reducing the number of alcohol equivalents to 1, reduced the regioselectivity to 2:1 (entry 3), highlighting the importance of excess alcohol in the reaction. An interesting find was that if 1 equivalent of reacting alcohol is added, along with 5 equivalents of a non-reactive alcohol (e.g. *tert*-butanol), the regioselectivity increases back to excellent levels (entry 4). The authors suggest this is a inexpensive and effective way to achieve the good regioselectivity of the reaction when using an expensive reactive alcohol.

Table 1.1. Effect of alcohol nucleophile equivalents on regioselectivity.



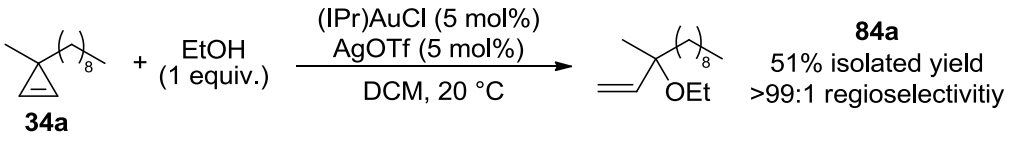
Entry	Equiv. of EtOH	84a:85
1	6	>99:1
2	3	>99:1
3	1	2:1
4	1 + 5 equiv of ^{t}BuOH	>99:1

In order to provide an explanation for why the excess alcohol is required to achieve excellent regioselectivities, the authors performed control reactions (Scheme 1.23). The first control reaction involved resubjecting a *tert*-allylic ether **84b** to the original gold(I)-catalysed reaction conditions (including 5 equivalents of nucleophile alcohol): no reaction was observed. The reaction was repeated once again, but *without* any additional nucleophile alcohol present. In this case, the *tert*-allylic ether **84b** underwent isomerisation to the primary allylic ether **86**. Thus, the excess alcohol in the reaction must suppress the isomerisation of tertiary to primary allylic ether.



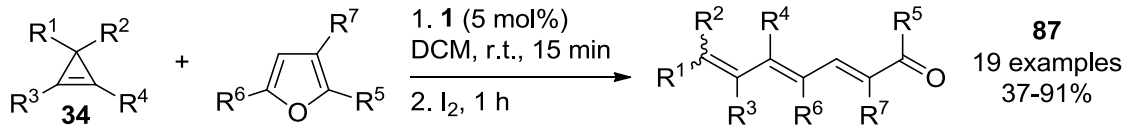
Scheme 1.23. Isomerisation control reactions of *tert*-allylic ether **84b**.

This observed isomerisation was found to be very much dependent on the gold(I) catalyst. The use of an NHC-gold(I) catalyst resulted in no isomerisation of a tertiary allylic ether to the corresponding primary isomer. Therefore, the authors investigated the use of an NHC-gold(I) as the catalyst in the reaction, but with only added 1 equivalent of nucleophile alcohol (Scheme 1.24). The reaction produced solely the *tert*-allylic ether **84a**, albeit with a lower isolated yield (51% *vs.* 83% with PPh_3AuNTf_2). However, it shows that in cases where regioselectivity is not as high as desired using the standard conditions from Scheme 1.21, the NHC-gold(I) catalyst may be used as an alternative method.



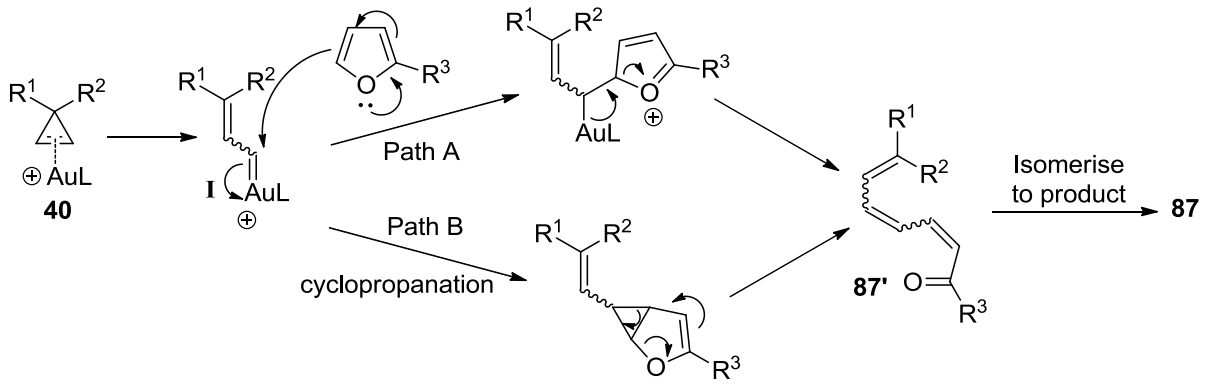
Scheme 1.24. Regioselective formation of *tert*-allylic ether with NHC-gold(I) catalyst.

Lee and co-workers further developed their intermolecular gold(I)-catalysed reactions with cyclopropenes, by extending their nucleophile scope to include furans (Scheme 1.25).[48] Cyclopropenes **34** were found to react with furans, affording conjugated triene products **87**. The furan addition to the cyclopropene is complete after 15 minutes, however a crystal of iodine is added to the reaction mixture to ensure complete isomerisation to the thermodynamically favoured *E*,*E*,*E*-isomer.



Scheme 1.25. Gold(I)-catalysed formation of conjugated trienes.

The proposed mechanism of formation (Scheme 1.26) initiates with the gold(I) catalyst facilitating cyclopropene ring-opening to the resonance intermediate **I**, as proposed in the alcohol addition mechanism (**Ia-c**) (Scheme 1.22). Nucleophilic attack of the furan then occurs, followed by opening of the furan ring to afford a mixture of triene isomers **87'** (path A). Alternatively, path B could operate where cyclopropanation occurs (*via* gold-carbene-type behaviour), which upon ring-opening will liberate a mixture of triene isomers **87'**. On addition of iodine, the mixture of isomers will isomerise to the most thermodynamically stable species **87** (*E*,*E*,*E*-isomer).



Scheme 1.26. Proposed mechanism for the gold(I)-catalysed formation of trienes.

Although there has been significant developments in the use of gold(I) catalysis with cyclopropenes, there is still an exciting amount of potential reactions to be investigated. The following two chapters discusses the results obtained from further development of the gold(I)-catalysed addition of nucleophiles to cyclopropenes.

1.4 References

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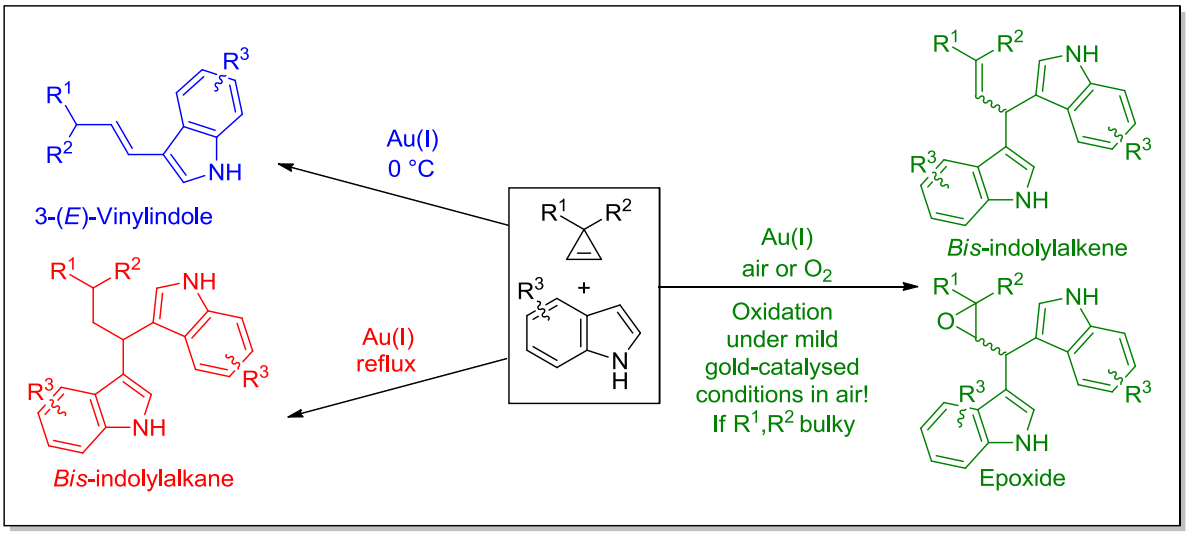
Chapter 2 – Gold(I)-Catalysed Addition of Indoles to 3,3-Disubstituted Cyclopropenes



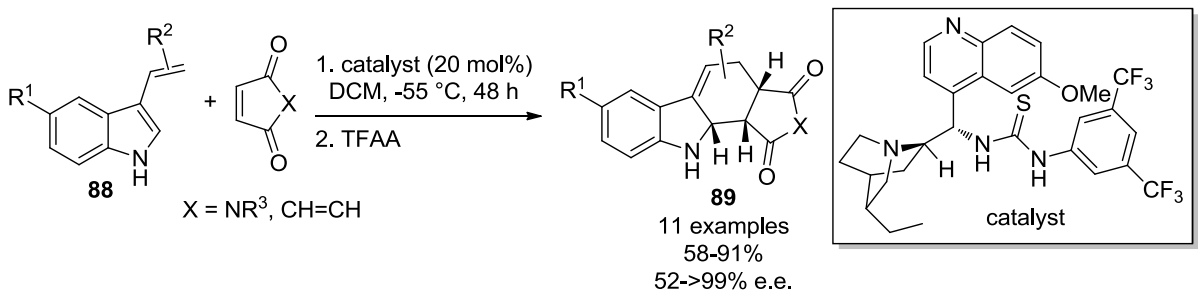
Acknowledgements: The author would like to thank Max Hadfield (PhD student) for initial studies into this work, and for the preparation of cyclopropene **34g**. Kristina Macleod and Lynn Arrowsmith (MChem project students) are gratefully acknowledged for optimisation studies into the unexpected oxidation products, and the preparation of cyclopropene **34h**. The author would also like to express thanks to Richard Mudd (MChem project student) for the synthesis of cyclopropenes **34e** and **34f**, and Ursula Paul (Erasmus project student) for the preparation of cyclopropene **34c**.

2.1 Introduction

2.1.1 3-Vinylindoles & *bis*-Indolylalkanes

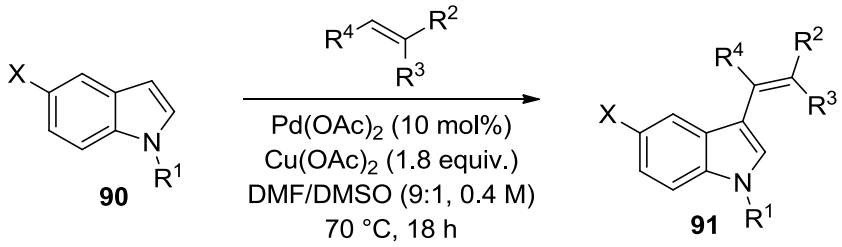
Indoles are found in a wide range of naturally occurring compounds, and molecules including the indole moiety have been used in a diverse range of pharmaceutical targets. The vinylindole unit has been used as an important synthetic building block,[1] giving access to a range of useful compounds which themselves can go on to produce biologically active molecules, such as indole alkaloids[2, 3] and carbazoles.[4] For example, structures that include a 3-vinylindole[5-8] component **88** have been shown to undergo [4+2] cycloadditions as dienes, in the synthesis of polycyclic heterocycles.[9-11]

Indeed, a recent example of a 3-vinylindoles reacting as dienes was reported by Ricci and co-workers in 2008 (Scheme 2.1).[9] The 3-vinylindoles **88** reacts with maleimides and quinones under organocatalytic conditions to form carbazoles **89** in good yields and impressive enantioselectivities. This procedure was utilised in the synthesis of an intermediate toward tubifolidine, an alkaloid natural product.



Scheme 2.1. Organocatalysed Diels-Alder formation of carbazoles **89** by Ricci.

There have been several reported methods of constructing the 3-vinylindole motif into a molecule, including *via* Wittig reactions[12] and Brønsted acid catalysis.[13, 14] One notable procedure is the palladium-catalysed C-H functionalisation reaction of indoles **90** with alkenes reported by Gaunt and co-workers in 2005 (Scheme 2.2).[7]



Scheme 2.2. Palladium-catalysed formation of 3-vinylindoles by Gaunt.

It was reported that the selection of the solvent was crucial for the regioselectivity of the reaction; with polar solvents selectively forming the desired 3-vinylindole products (**91**), and 2-vinylindoles forming on the addition of acid to the reaction solvent.

Another interesting group of indole-containing compounds is the *bis*-indolylalkanes **92** (Figure 2.1). There have been examples reported of *bis*-indolylalkanes showing anticancer activity.[15] The relatively simple compound **93** has been demonstrated to significantly reduce the growth of lung, breast and renal cancer cells.[16]

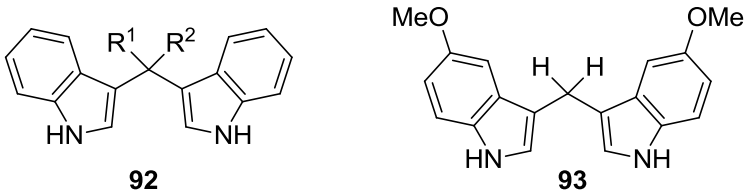
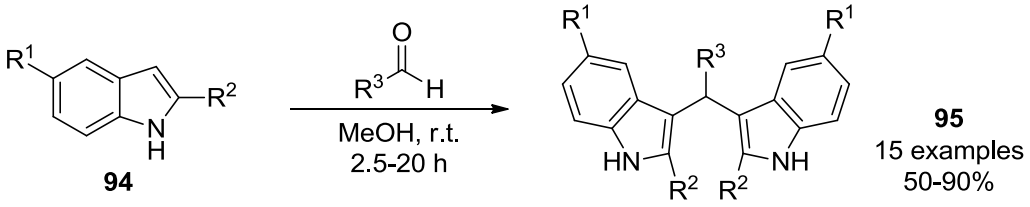


Figure 2.1. General *bis*-indolylalkane structure **92** and biologically active **93**.

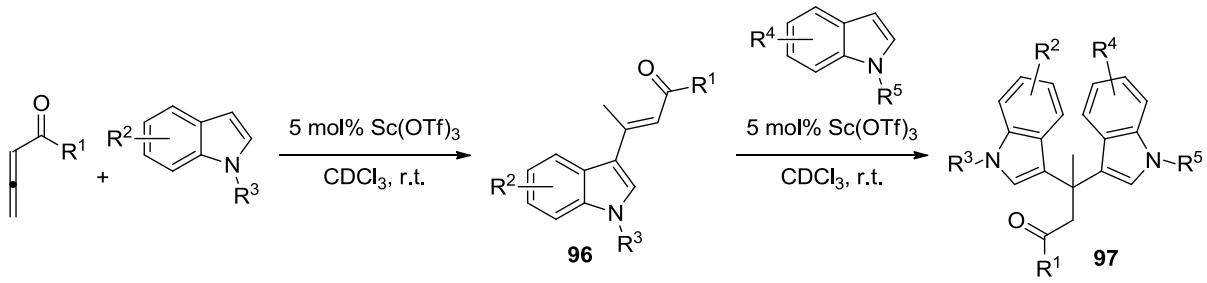
Perhaps the simplest known method to obtain *bis*-indolylalkanes is the condensation reaction of an aldehyde with indoles **94**.[17-19] In 2006, Bhuyan reported a highly efficient method, with the reaction being carried out in protic solvents at room temperature (Scheme 2.3).[17]



Scheme 2.3. Condensation of aldehydes and indoles by Bhuyan.

The method has a wide substrate scope, and was shown to work very well in both methanol and water as the reaction solvent. The aldehyde substrate can be aryl or alkyl-based, and even heterocycles are tolerated. If the reaction solvent was switched to acetonitrile, chloroform, tetrahydrofuran or toluene, no reaction took place, thus showing the reliance on protic solvents in the reaction. The protic solvents aid reactivity by forming hydrogen bonds with the aldehyde substrate, activating it toward nucleophilic attack from the indole.

One disadvantage to condensation reactions is that it is often difficult to achieve a mixed *bis*-indolylalkane (different substituents on each indole in **92**). To overcome this, Ma reported a scandium(III)-catalysed reaction in 2005 to attain these mixed species **97** from allenic ketones in a stepwise fashion, *via* the corresponding 3-vinylindole intermediate **96** (Scheme 2.4).[20]



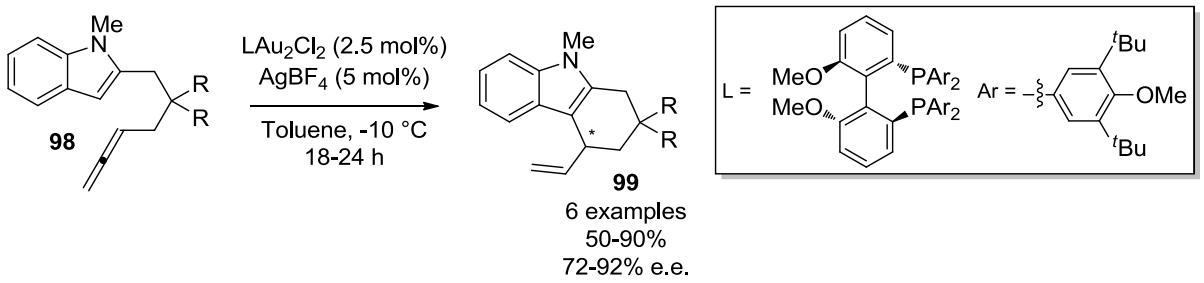
Scheme 2.4. Ma's Sc(III)-catalysed two-step formation of a mixed *bis*-indolylalkane.

Initially, one molecule of an indole will add to the allenic ketone, affording the β-indolyl-α,β-unsaturated (*E*)-enone **96**. If desired, the reaction can be stopped at this point, allowing the purification of this compound **96**. The formation of **96** was shown to be highly stereoselective (*E*:*Z* ratios all >99:1). Alternatively, if a second equivalent of another indole was added to **96**, the reaction would proceed to give the mixed *bis*-indolylalkane **97**. This was shown with 2 examples, giving yields of 46-57% over 2 steps. A related example of platinum-catalysed additions of indoles to allenes was also reported by Muñoz and co-workers.[21]

2.1.2. Gold(I)-Catalysis with Indoles

2.1.2.1 Intramolecular Reactions

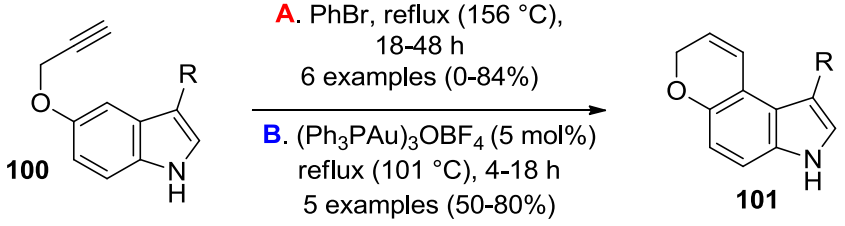
There are various reports in the literature of gold(I)-catalysed intramolecular reactions involving indoles.[22-28] The intramolecular hydroarylation of allenes **98** with indoles, yielding tetrahydrocarbazole **99**, was reported by Widenhoefer in 2007 (Scheme 2.5).[28]



Scheme 2.5. Gold(I)-catalysed intramolecular hydroarylation of allenes and indoles.

The hydroarylation reaction employs the use of a chiral gold(I) catalyst, allowing the enantioselective formation of product **99**. The method was found to be an effective method of installing six- and seven-membered rings with notable yields, it is also tolerant of alcohol functionality within the reacting substrate. This is impressive due to alcohols being known to react with allenes under gold(I)-catalysed conditions.[29]

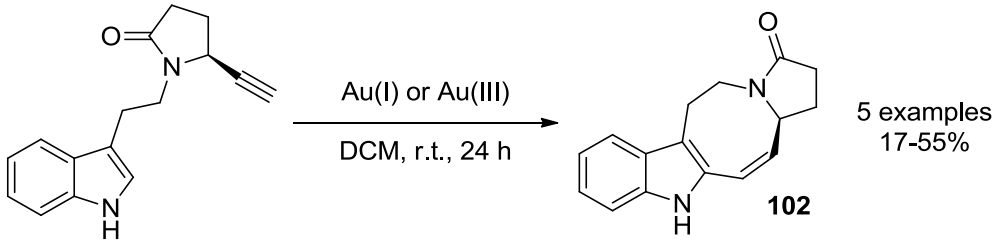
A study carried out by Macor into the synthesis of dihydropyrano[3,2-e]indoles **101**, demonstrated that the gold(I)-catalysed formation of the dihydropyran ring was much more efficient than the thermal Claisen rearrangement (Scheme 2.6).[26] The gold(I)-catalysed reaction involves activation of the alkyne **100**, intramolecular attack from the benzene ring, followed by rearomatisation and protodemetallation, affording **101**.



Scheme 2.6. Two different routes to dihydropyrano[3,2-e]indoles.

Conditions used for the thermal Claisen rearrangement (**A**) involves very high reaction temperatures (156 °C) and rather long reaction times (18-48 h). On the other hand **B** shows the gold(I)-catalysed reaction conditions. This alternative route requires shortened reaction times (4-18 h) and lower temperatures (101 °C). It can be seen that the gold(I)-catalysed reaction is superior to its alternative thermal rearrangement, signifying the power of gold catalysis over some well-established methods. These types of products **101** are used as serotonin analogues; hence this reaction could prove very useful for synthesis of certain pharmaceutical molecules.

An example of gold catalysis being potentially used in the synthetic route to an indole-containing natural product was reported by Echavarren in 2009.[24] The devised strategy of employing gold catalysis as the key cyclisation step in the formation of lundurines tetracyclic core skeleton **102** is outlined in Scheme 2.7. It involves the hydroarylation of an alkyne bond, cyclising in an 8-*endo-dig* fashion.

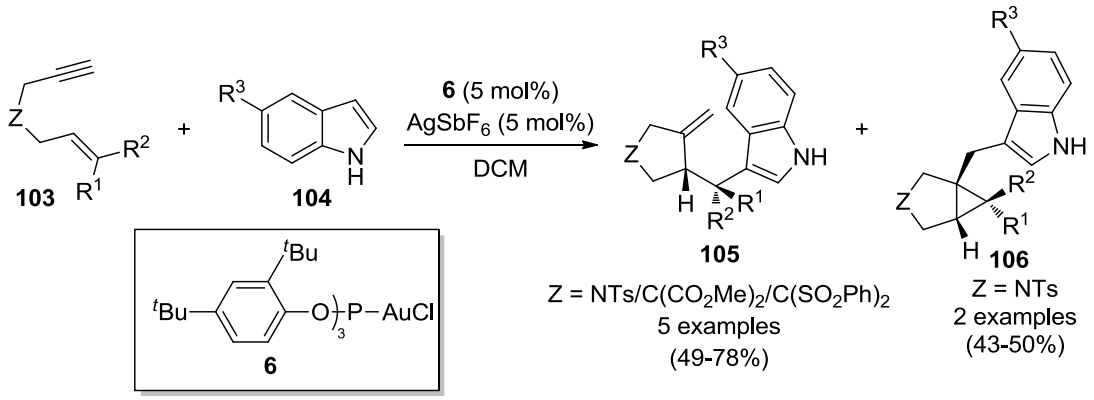


Scheme 2.7. Gold-catalysed cyclisation step to form tetracycle.

2.1.2.2 Intermolecular Reactions

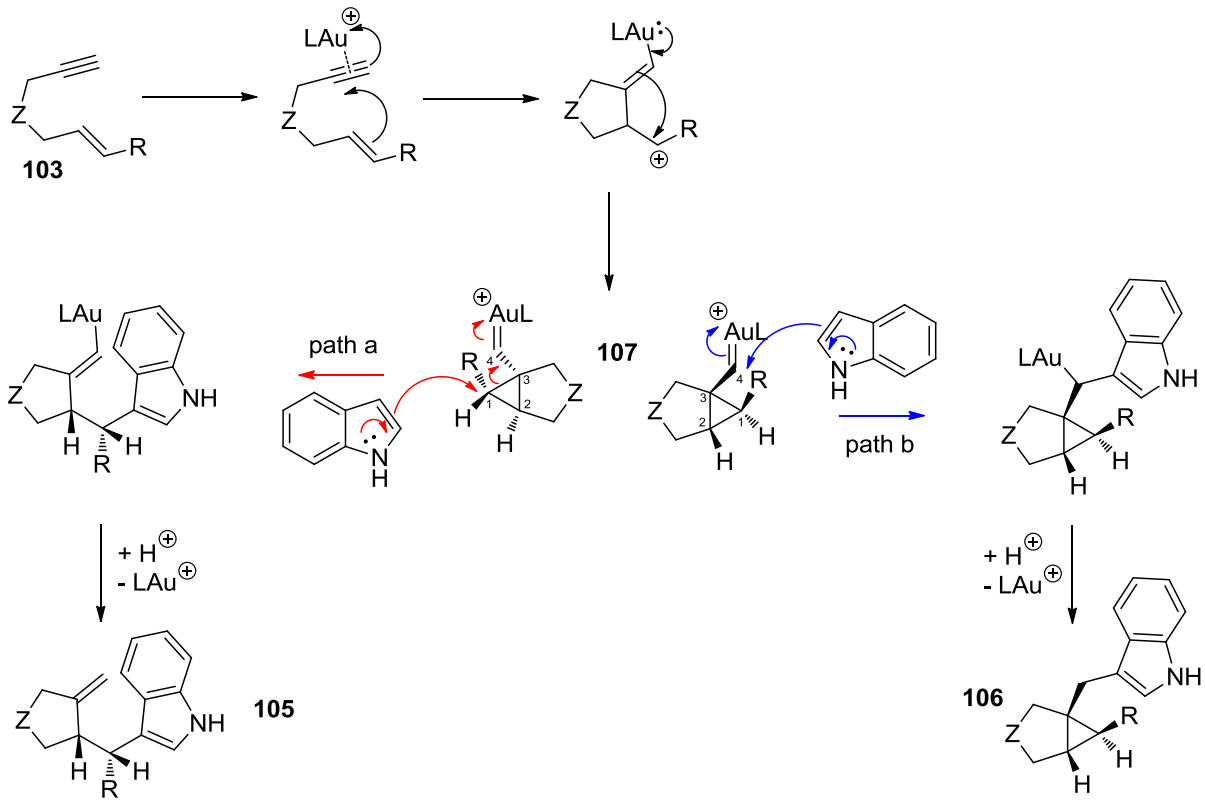
The gold(I)-catalysed intramolecular reactions with indoles are an excellent way of building up polycyclic heterocycles, however it is also desirable to develop *intermolecular* procedures involving indole additions to electrophiles through gold(I)-catalysis. Within the last decade, there has been a vast array of reported reactions that show the intermolecular addition of indole using gold(I)-catalysis can be remarkably efficient and high yielding.[30-38]

Indoles have been used in trapping intermediates in gold(I)-catalysed enyne cyclisation reactions.[36-38] Addition of indoles **104** to 1,6-enynes **103** were reported by Echavarren and co-workers, showing that two different products could arise (Scheme 2.8).[37] Alkene **105** and cyclopropane **106** are both formed from the same starting material, through the proposed mechanisms shown in Scheme 2.9.



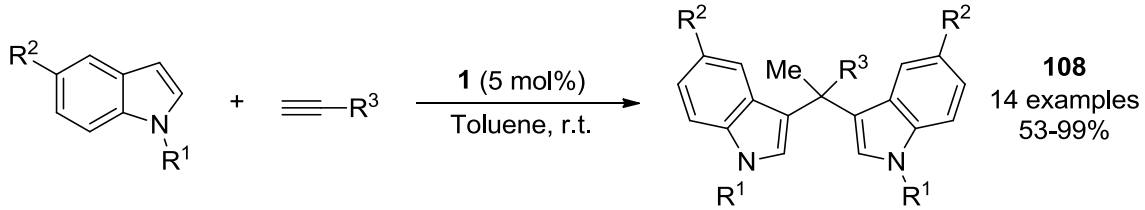
Scheme 2.8. Gold(I)-catalysed indole addition to 1,6-enynes.

The gold catalyst selectively activates the alkyne triple bond in **103**, allowing a 5-*exo*-dig cyclisation. The resulting cyclopropyl gold-carbene intermediate **107** can then undergo nucleophilic attack by indole. Alkene **105** is formed through indole attack at the C1 position. Cyclopropane derivative **106** is obtained through indole attack at the carbene carbon C4. The final products are released after protodemetallation of the gold(I)-species, regenerating the active catalyst. Site selectivity can be controlled in some cases with the choice of ligand on the gold(I) catalyst, with NHC-catalysts favouring attack the the C4 position of intermediate **107**.



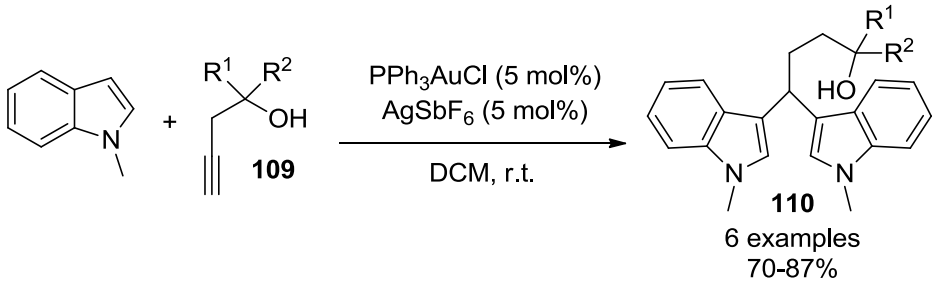
Scheme 2.9. Proposed mechanism for gold(I)-catalysed indole additions to 1,6-enynes.

Another paper published by Echavarren highlighted the intermolecular addition of indoles to terminal alkynes, forming *bis*-indole products **108** (Scheme 2.10).[30] Single regioisomers were obtained for all examples in good to excellent yields. The reaction was found to be compatible with alkyl-subsituted alkynes, which was previously reported as not possible with gallium(III)-catalysed reactions of the same substrates.[39]



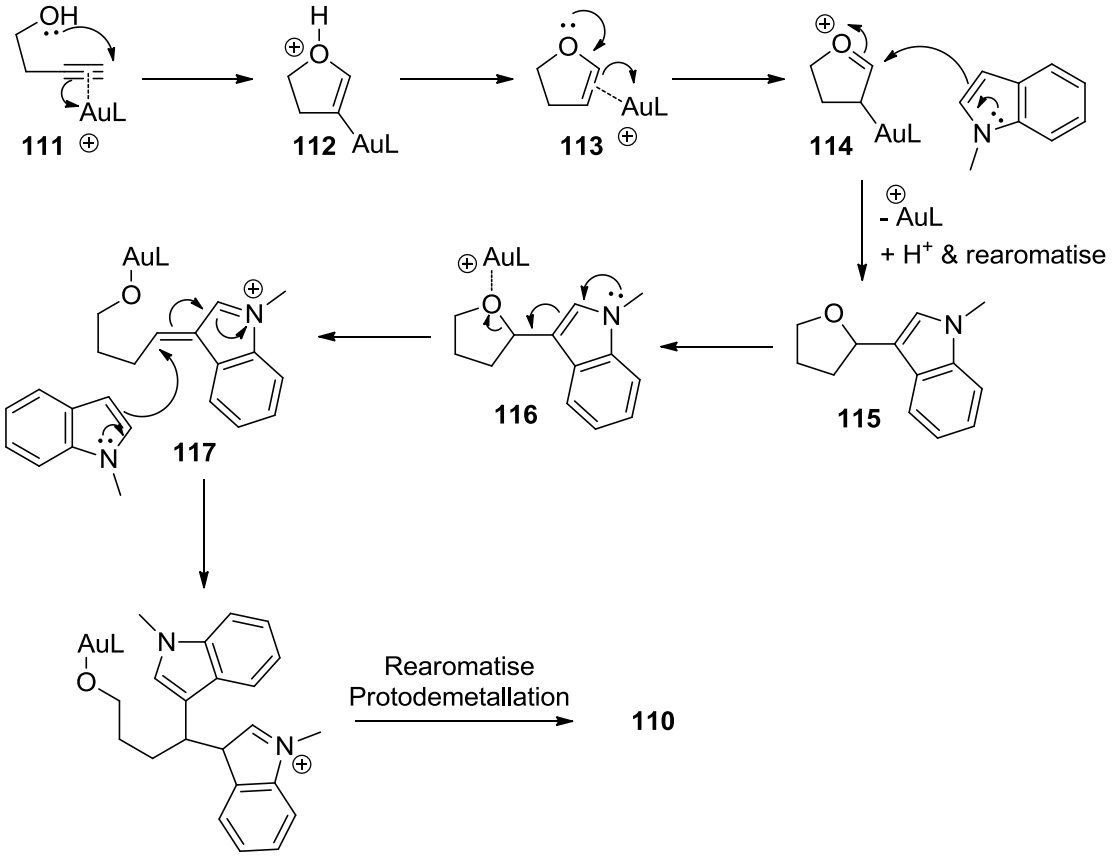
Scheme 2.10. Gold-catalysed formation of *bis*-indoles.

In 2009, Barluenga and co-workers reported their findings of a novel route to *bis*-indolylalkanes **110** from the gold-catalysed addition of *N*-methylindole to the terminal carbon of 3-butyn-1-ol derivatives **109** (Scheme 2.11).[31] The reaction conditions are very mild (room temperature), allowing the authors to recommend this reaction for natural product synthesis.



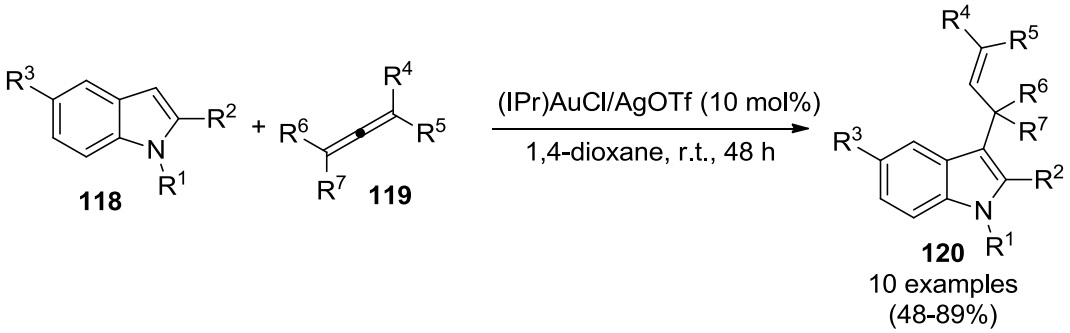
Scheme 2.11. Formation of *bis*-indolylalkanes by Barluenga.

The mechanism of formation was proposed by Barluenga, with the internal alcohol group directing the gold catalyst (Scheme 2.12). The active gold(I) catalyst is formed *in situ* and will activate the unsaturated bond of the 3-butyn-1-ol (**111**). A ring-closing reaction can then occur from intramolecular attack of the alcohol, the resulting species **112** can undergo protodemetallation, yielding intermediate **113**. The gold(I)-species can then reactivate the substrate allowing nucleophilic attack by the indole (**114**). Rearomatisation and protodemetallation occurs, releasing intermediate **115**. The catalyst can then activate the substrate once more through coordination to the oxygen (**116**). Nucleophilic attack by indole can occur once again on **117**, affording desired product **110** after rearomatisation and protodemetallation.



Scheme 2.12. Proposed mechanism for the formation of *bis*-indolylalkanes.

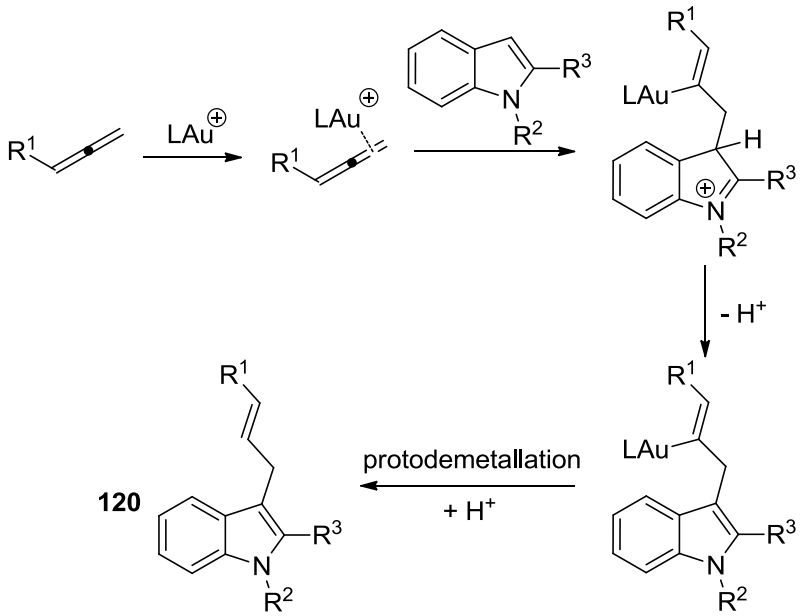
Indoles were shown to undergo intermolecular hydroarylation with allenes, producing 3-allylindoles **120** (Scheme 2.13).[33] Widenhoefer and co-workers revealed that this reaction was possible with a range of indole derivatives **118** with mono-, 1.3-disubstituted and tetrasubstituted allenes **119**.



Scheme 2.13. Gold(I)-catalysed synthesis of 3-(*E*)-allylic indoles.

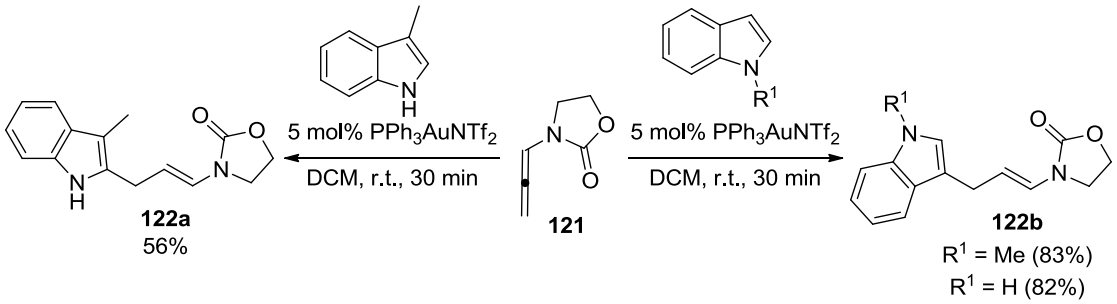
The reaction is carried out at room temperature and only one product is observed. The sole product, 3-(*E*)-allylic indole **120**, demonstrates that the reaction proceeds with high regioselectivity and stereoselectivity. Scheme 2.14 shows the proposed mechanism of the reaction. The selectivity is rationalised by the addition of the active gold(I)-species *cis* to the R^1 group and the subsequent indole attack.

It is worth noting that this reaction generally requires more nucleophilic indoles, such as 1,2-dimethylindoles. The reactivity of gold(I)-activated allenes towards indoles could explain this; previously Gagné had reported that indole addition to allenes was not possible.[40] The enantioselective version and DFT calculations were also reported by Che and co-workers in 2011.[41]



Scheme 2.14. Proposed mechanism for the formation of 3-allylindoles.

A gold(I)-catalysed reaction reported by Kimber in 2010 demonstrated how allenamide **121** undergoes arylation with indoles to produce allylic indole enamides **122a**/**122b** (Scheme 2.15).[35] The reaction is very mild (room temperature) and full conversion was achieved after a short 30 minute period.

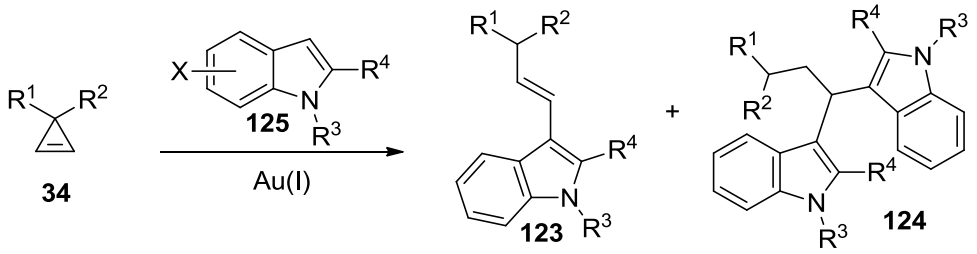


Scheme 2.15. Gold-catalysed arylation of allenamides.

Selectivity could be altered through blocking the C3 position on the indole. Using C3-unsubstituted indoles, allylic indole enamines **122b** were formed. However, when 3-methylindole was used as the indole substrate, the C3 position is no longer available to take part in the reaction. Instead, the selectivity switches to allow reactivity at the C2 position, giving allylic indole enamine **122a**.

2.2 Project Aim

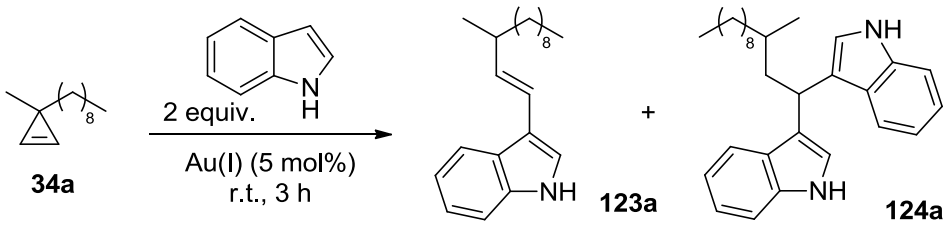
One of the key research areas in the Lee Group is the development of novel gold(I)-catalysed reactions with cyclopropenes **34**. To date within the group, cyclopropenes have been shown to react with a number of nucleophiles under gold(I)-catalysed conditions, including alcohols[42, 43] and furans.[44] Initial results carried out by M. S. Hadfield (PhD student) suggested that indoles could be used as effective nucleophiles in gold(I)-catalysed additions to cyclopropenes (Scheme 2.16).



Scheme 2.16. Two products from gold(I)-catalysed additions of indole to cyclopropenes.

The initial experiments carried out showed that two products could be obtained from the reaction; 3-(*E*)-vinylindoles **123** and *bis*-indolylalkanes **124**. It was demonstrated that the ratio of these two products could be controlled through the use of different catalysts (Table 2.1).

Table 2.1. Initial gold(I)-catalysed indole addition results.



Entry	Catalyst	Solvent	Ratio 124a:123a[a]	Yield
1	PPh_3AuNTf_2	DCM	80:20	53% **124a**
2	PPh_3AuNTf_2	Toluene	96:4	52% **124a**
3	**1**	DCM	3:97	42% **123a**
4	**1**	Toluene	50:50	Not Isolated

[a] Determined by ^{1}H NMR analysis of the crude mixture.

The use of PPh_3AuNTf_2 as the gold(I) species favoured the formation of *bis*-indolylalkane **124a** (entries 1 & 2), the ratio of which could be further improved by switching from DCM to toluene as the reaction solvent (entry 1 *vs*. entry 2). Conversely, if the cationic gold(I) catalyst **1** was used, the reaction product switches to the 3-(*E*)-vinylindole **123**. The reaction is highly selective, with only the *E*-isomer observed. The yield of **123a** is not improved by using toluene as the reaction solvent, therefore further optimisation was required.

These initial results laid the foundations for this project, and a fully *controllable* reaction was desired; to achieve either 3-(*E*)-vinylindoles **123** or *bis*-indolylalkanes **124** *selectively* simply by changing the reaction conditions. To accomplish this, a series of optimisation studies were required to be undertaken, to control either the production of **123** or **124** selectively.

Once a fully switchable reaction has been developed, the overall scope of the reaction was to be examined. This would involve looking at both cyclopropene and indole substrates, with varying functional groups and steric bulk.

The mechanism of the reaction was also to be probed. Completing these mechanistic studies would provide evidence of how the products are formed, and whether the *bis*-indolylalkane **124** is the result of further reaction of the 3-(*E*)-vinylindole **123**.

2.3 Results & Discussion

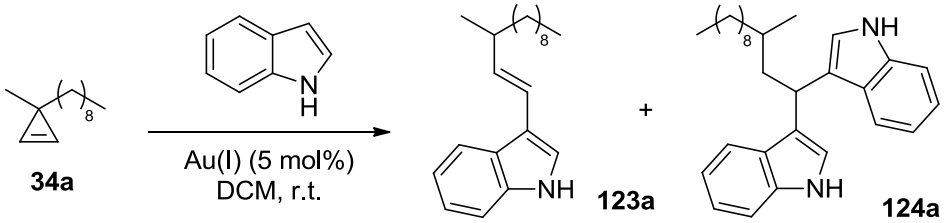
2.3.1 3-(*E*)-Vinylindoles

2.3.1.1 Reaction Optimisation

On the basis of the initial results carried out by M. S. Hadfield (PhD student), within the Lee Group, it was decided that a catalyst screen would be most beneficial as a starting point of the optimisation. The initial results suggested that the attainable products **123** and **124** could be controlled by changing the catalyst, therefore a range of catalysts and counterions were screened (Table 2.2). To enable a more efficient screening process, isolated yields were not obtained, and instead NMR yields were calculated by comparison to an internal standard (dimethyl sulfone).

A major challenge was the isolation and purification of the desired 3-(*E*)-vinylindoles **123**, these alkyl substituted compounds are known to readily decompose on purification/standing.[5] In addition to the stability of compounds **123**, another issue was the separation of the product from the indole starting material.

Table 2.2. Catalyst screen of gold(I)-catalysed addition of indole to cyclopropene.



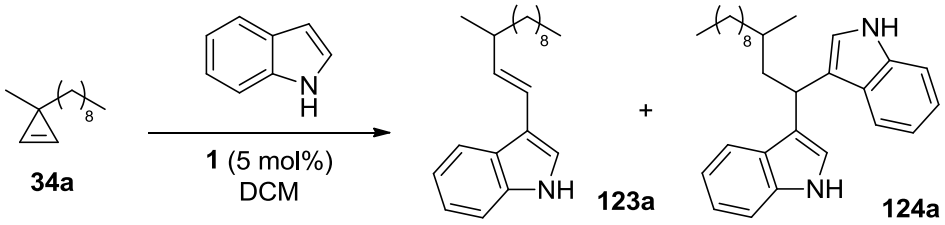
Entry	Catalyst	Equiv. Indole	Time (h)	Ratio 123a:124a[a]	Yield 123a,[b,c]
1	PPh_3AuNTf_2	1	3	N/D	25%
2	$PPh_3AuCl/AgOTf$	0.66	3	N/D	9%
3	(IPr)AuCl/AgOTf	0.66	3	60:40	23%
4	$(IPr)AuCl/AgSbF_6$	0.66	4	40:60	12%
5	(IPr)AuCl/AgOTs	0.66	4	66:33	8%
6	$(IPr)AuCl/AgBF_4$	0.66	4	40:60	5%
7	**1**	0.66	3	75:25	50%

[a] Determined by ^1H NMR analysis of the crude mixture. [b] NMR yield by comparison with an internal standard (dimethyl sulfone). [c] Full consumption of cyclopropene.

The commercially available active gold(I)-catalyst, PPh_3AuNTf_2, gave a low yield of 25% (entry 1), however the yield was reduced significantly to 9% when the counterion was changed to the more coordinating OTf (entry 2). Selecting the NHC-based catalyst, (*in situ* formed (IPr)AuOTf), improved the yield to 23% of **123a**, but the ratio of **123a**:**124a** was disappointing (entry 3). No valuable improvements were observed from altering the counterion of the (IPr)Au(I) species (entries 3-6). Switching the catalyst to the commercially available cationic **1** showed a major increase in both yield and ratio (entry 7). This catalyst was taken forward to be used in further studies.

With the most promising catalyst selected, a range of experiments were completed by varying time, temperature and number of indole equivalents (Table 2.3). Due to the inseparability of the product **123a** from the starting material indole, keeping the number of indole equivalents to as low as possible was highly desired.

Table 2.3. Screen of time, temperature and indole equivalents.



Entry	Equiv. Indole	Time (h)	Temperature (°C)	Ratio 123a:124a[a]	Yield 123a[b,c]
1	0.66	0.5	20	70:30	43%
2	2	3	20	88:12	59%
3	2	1	20	91:9	68%
4	2	3	10	85:15	66%
5	1	3	0	81:19	52%
6	3	3	0	91:9	68%
7	2	1	0	88:12	59%
8	2	2	0	91:9	75%
9	2	3	0	>95:5	91%[c]

[a] Determined by ^{1}H NMR analysis of the crude mixture. [b] NMR yield by comparison with an internal standard (dimethyl sulfone). [c] Reaction performed in triplicate. [c] Full consumption of cyclopropene.

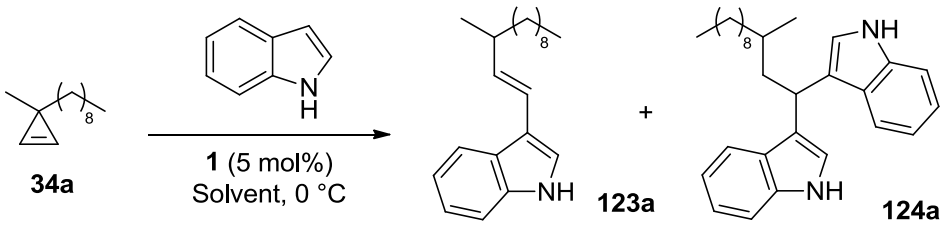
As shown in Table 2.3, reducing the temperature of the reaction was greatly beneficial to the overall yield of the reaction; decreasing from 20 °C to 10 °C improved the yield from 59% to 66% (entries 2 & 4). Lowering the temperature further to 0 °C increased the yield of **123a** to an impressive 91%, with an excellent **123a**:**124a** ratio of >95:5 (entry 9).

Altering the number of indole equivalents gave interesting, and perhaps unexpected results. Utilising 1 equivalent of indole afforded a mediocre yield of 52% and good ratio of 81:19 (entry 5). Increasing the indole equivalents to 2 gave the excellent results described above (entry 9), this was surprising to us as our initial thought on increasing the indole equivalents, was that the yield of **124a** would increase, since two equivalents are required to form this product. However when the number of indole equivalents is raised to 3, the yield diminishes (entry 6). A poorer yield of 68% is observed along with a slight reduction in ratio to 91:9 (entry 6). Therefore, it appears that using 2 equivalents of indole is necessary to achieve an excellent yield and product ratio in favour of **123a**.

Moving our attention to reaction time, it was found that both the yield and ratio of products improved with increased time (entries 7-9). A moderate yield of 59% was attained when the reaction was left for 1 hour (entry 7). The yield was significantly enhanced by raising the reaction time to 2 hours and 3 hours, giving 75% and 91% respectively (entries 8 and 9).

Unfortunately, no conditions could be found that produced excellent yields and ratios of products without the use of excess indole. *Alkyl* substituted 3-vinylindoles are known to have limited stability and will decompose readily.[5] Repeated attempts at silica, triethylamine buffered silica, alumina and florisil chromatography all resulted in partial decomposition and any isolated vinylindoles **123** would begin to decompose within <1 day. Consequently, NMR yields by comparison with an internal standard were continued to be reported, with a separate procedure for product isolation (See 2.5 Experimental Section). Currently the best conditions for the production of **123a** was using **1** (5 mol%) with 2 equivalents of indole, at 0 °C for 3 hours. These conditions were already very mild and effective, however it was desirable to test reaction solvents and attempt to lower the catalyst loading. A very short screen of reaction solvents was performed (Table 2.4).

Table 2.4. Short solvent screen.



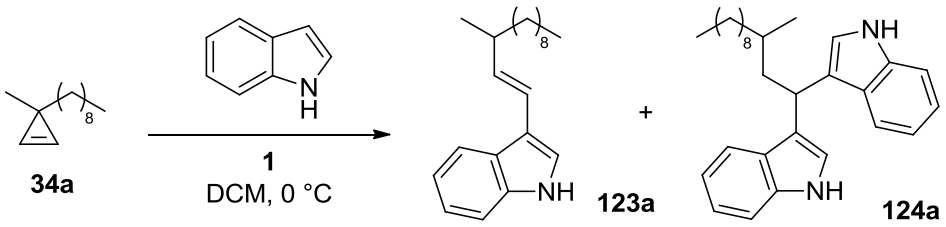
Entry	Equiv. Indole	Solvent	Time (h)	Ratio 123a:124a[a]	Yield 123a[b,c]
1	2	MeCN	3	93:7	79%
2	2	DMF	3	N/D[d]	50%
3	1	MeCN	5	89:11	8%
4	0.66	MeCN	5	88:12	30%
5	2	DCM	3	>95:5	91%

[a] Determined by ^{1}H NMR analysis of the crude mixture. [b] NMR yield by comparison with an internal standard (dimethyl sulfone). [c] Full consumption of cyclopropene. [d] Could not be determined due to messy spectrum.

Switching the reaction solvent to acetonitrile gave an excellent product ratio, but a reduced yield of 79% (entry 1 *vs.* entry 5). When the equivalents of indole are altered with acetonitrile, a severe reduction in product yield is observed (entries 3 & 4). Highly polar solvent DMF produced a yield of 50% of **123a**, although the spectrum was not as clean as when using DCM, therefore was not investigated further. From this very short study, no conditions were found to match or better those previously established (entry 5).

In a final attempt to find a method that proceeds with complete consumption of the indole starting material, a screen of catalyst loading was performed (Table 2.5). It was hoped that by using 0.9 equivalents of indole, the reaction would proceed to full conversion and allow for isolation of product **123a**.

Table 2.5. Catalyst loading and portion-wise addition screen.



Entry	Catalyst Loading	Time (h)	Ratio 123a:124a[a]	Yield 123a[b,c]
1	5 mol% + 5 mol% after 5 h	7	>95:5	51%
2	5 mol% + 5 mol% after 5 h	24	>95:5	53%
3	1.5 mol% + 1.5 mol% after 3 h	6	>95:5	60%
4	1.5 mol% + 1.5 mol% + more **34a** after 3 h	6	>95:5	52%
5	1 mol%	6	>95:5	64%
6	1 mol%	15	>95:5	58%
7	10 mol%	24	>95:5	42%

[a] Determined by ^{1}H NMR analysis of the crude mixture. [b] NMR yield by comparison with an internal standard (dimethyl sulfone). [c] Full consumption of cyclopropene.

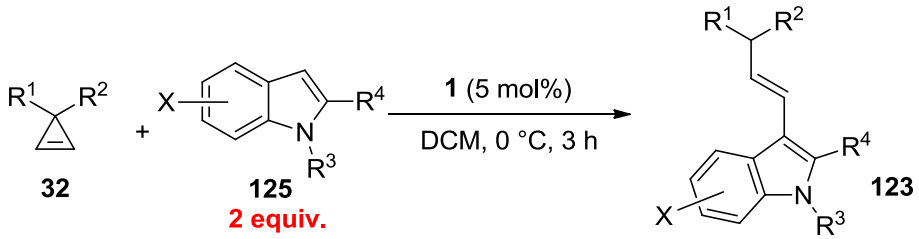
The addition of more catalyst to the reaction did not show any improvement to the yield of product **123a** (entries 1 & 2). Adding a second portion of 5 mol% Au(I) catalyst after 5 hours resulted in relatively moderate yields (51-53%), even when left to react for a full 24 hours (entries 1 & 2). However, entry 2 had no remaining indole starting material in the ^{1}H NMR spectrum of the crude mixture, whereas entry 1 did.

Decreasing the catalyst loading to two portions of 1.5 mol% did show a slight improvement to the reaction. An increase in yield to 60% was observed (entry 3), however starting material indole was observed in the crude mixture. Modifying this procedure slightly by adding slightly more cyclopropene **34a** to the reaction at the same time as the second portion of catalyst decreased the yield of the reaction, although no traces of starting material indole were observed (entry 4).

Lowering the catalytic loading to 1 mol% did show an improvement in yield to 64% (entry 5), but leaving the reaction for longer resulted in a diminished yield of 58% (entry 6). Finally, the catalyst loading was increased to 10 mol% (added in one portion)

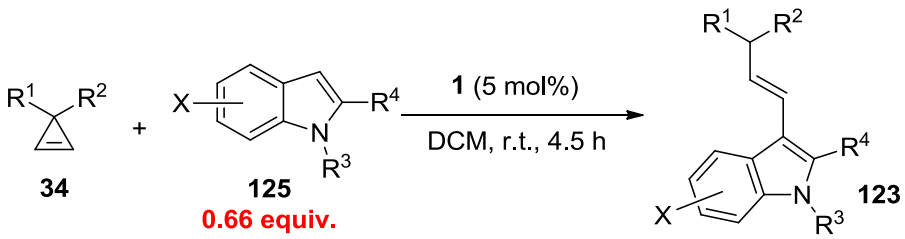
and a notable decrease in yield was observed (entry 7). Disappointingly, none of these methods were found to be viable in achieving isolation of vinylindole product **123** in high yields.

Due to the instability of alkyl substituted 3-(*E*)-vinylindoles **123**, two procedures were chosen for this project. The first procedure allowed for the optimised conditions to be utilised, achieving high yields and excellent product selectivity (Scheme 2.17). Since this method employed the use of 2 equivalents of indole substrate, the products could not be isolated for accurate yield determination due to decomposition of **123** upon chromatography (*vide supra*). Hence, yields were calculated by comparison to an internal standard (dimethyl sulfone).



Scheme 2.17. Optimised conditions for formation of 3-(*E*)-vinylindoles.

To allow full characterisation of these products, a separate procedure was selected (Scheme 2.18). This different procedure used the indole substrates as the limiting reagent, and therefore no traces of indole were observed in the ^{1}H NMR spectrum of the crude mixture. Purification could then be carried out very quickly (to limit decomposition of the products), to gain enough pure material for characterisation purposes.

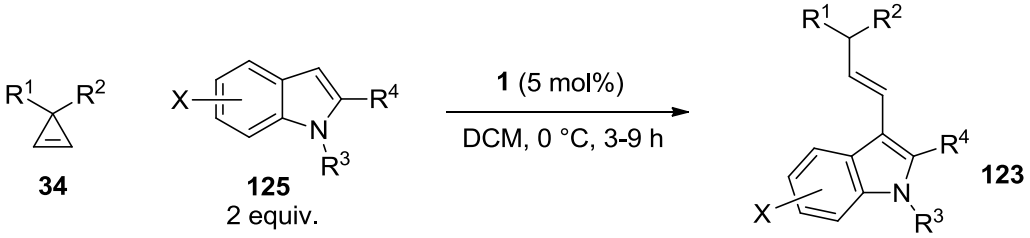


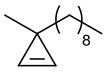
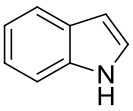
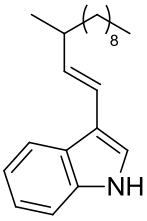
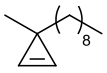
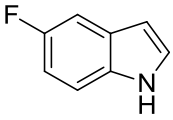
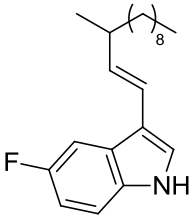
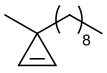
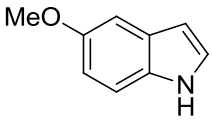
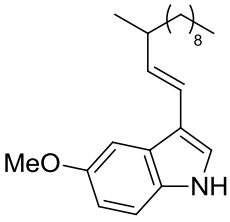
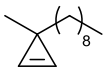
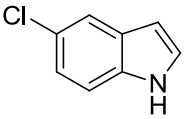
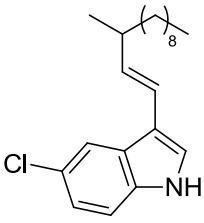
Scheme 2.18. Synthetic procedure for the isolation of 3-(*E*)-vinylindoles.

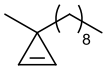
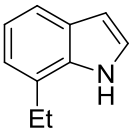
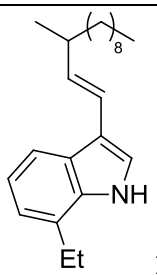
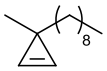
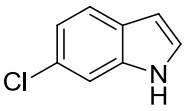
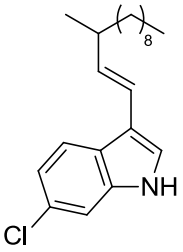
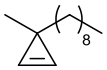
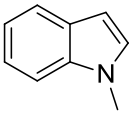
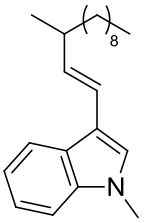
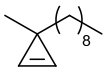
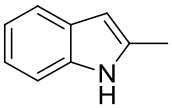
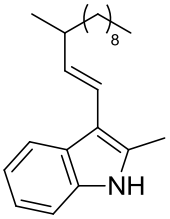
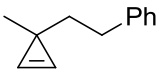
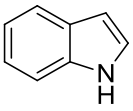
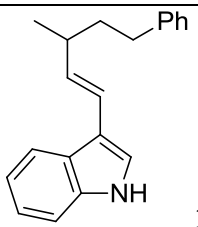
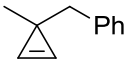
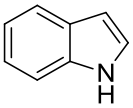
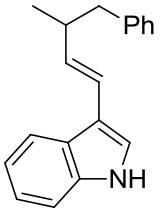
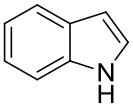
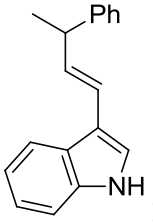
2.3.1.2 Reaction Scope

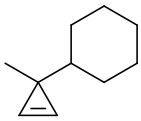
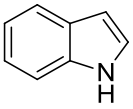
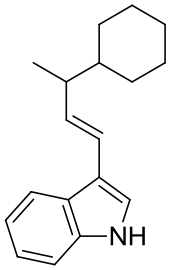
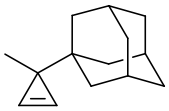
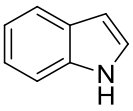
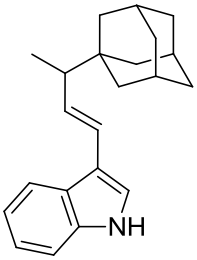
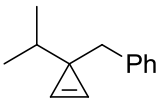
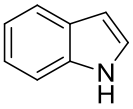
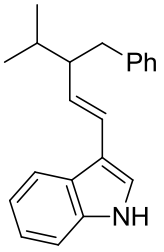
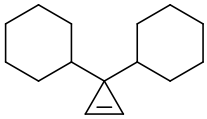
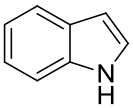
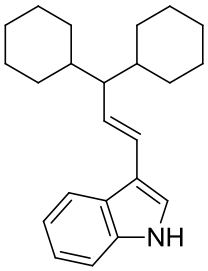
With the optimised conditions in hand, the scope and generality of the reaction was explored. A range of indole **125** and cyclopropene **34** substrates were used in the reaction (Table 2.6).

Table 2.6. Gold(I)-catalysed synthesis of 3-(*E*)-vinylindoles.



Entry	34	Indole 3	Product	Yield[a]
1	 **34a**	 **125a**	 **123a**	91%
2	 **34a**	 **125b**	 **123b**	72%
3	 **34a**	 **125c**	 **123c**	65%
4	 **34a**	 **125d**	 **123d**	77%[c]

5	 **34a**	 **125e**	 **123e**	66%
6	 **34a**	 **125f**	 **123f**	63%
7[b]	 **34a**	 **125g**	 **123g**	91%
8	 **34a**	 **125h**	 **123h**	64%
9[b]	 **34b**	 **125a**	 **123i**	81%
10[b]	 **34c**	 **125a**	 **123j**	73%
11[d]	 **34d**	 **125a**	 **123k**	83%

12	 **34e**	 **125a**	 **123l**	70%[e]
13	 **34f**	 **125a**	 **123m**	81%[e]
14[d]	 **34g**	 **125a**	 **123n**	28%[f]
15	 **34h**	 **125a**	 **123o**	7%[g]

[a] NMR yield by comparison to an internal standard. [b] 1-1.05 equiv. **125** used. [c] Reaction time 16.5 h. [d] 5 equiv. **125** used. [e] Trace side products **126**/**127**. [f] Products **126a** (15%) and **127a** (28%). [g] Products **126b** (18%) and **127b** (10%).

Cyclopropene **34a** was selected to react with a range of indoles. The reaction was found to proceed well with both electron-withdrawing and electron-donating indoles (entries 2-6). The indoles with electron-withdrawing substituents fared slightly better than those with electron-donating groups (entries 2, 4 & 6 *vs*. entries 3 & 5). The products of indoles **125d** and **125f** leave the chloro-group untouched, providing a handle for further functionalisation (entries 4 & 6).

In some cases, the number of equivalents of indole could actually be lowered to 1-1.05 equivalents (entries 7, 9 & 10). *N*-methylindole **125g** was found to react efficiently with 1.05 equivalents to afford an excellent 91% yield of **123g** (entry 7). Likewise, using cyclopropenes **34b** and **34c** the number of indole equivalents could be reduced without a reduction in product yield (entries 9 & 10).

As well as the screen of various indoles, the cyclopropene substrate scope was also investigated (entries 9-15). Cyclopropene **34d** was found to react well to give a very good 83% yield of **123k** (entry 11), previously it had been shown that having a phenyl substituent can cause an intramolecular rearrangement.[42, 43, 45, 46] However only product **123k** was observed in this reaction, although 5 equivalents of indole were required to avoid this rearrangement. Increasing the steric bulk of one of the substituents on the substrate, for example to cyclohexyl- or adamantyl-groups, exhibits the same good reactivity with no reduction in overall yield (entries 12 & 13). Yet when both R^1 and R^2 are sterically encumbered, a huge reduction in yield is observed (entries 14 & 15).

This large reduction in yield with the bulky cyclopropene substrates can be attributed to unexpected side-products being formed in the reaction. On purification of the crude reaction mixture, *bis*-indolylalkene **126** and epoxide **127** were found to be present (Figure 2.2). These products are never observed with non-bulky cyclopropene substituents, and only appear as the steric bulk of the 3,3-disubstitution increases. The products are highly unexpected as their structures suggests that an oxidation must take place during the reaction, which is extremely rare in homogeneous gold(I)-catalysis (*vide infra*).[46-49]

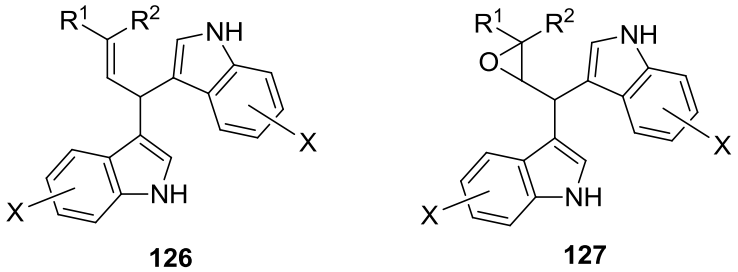


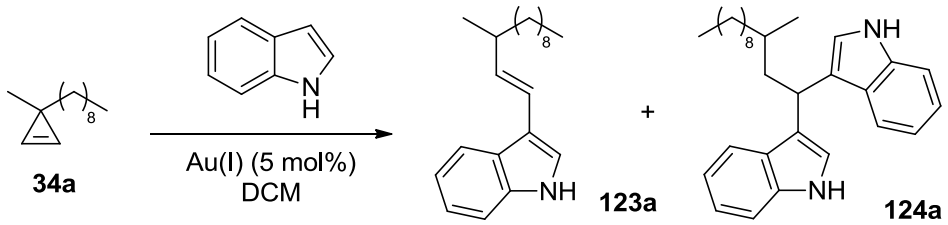
Figure 2.2. Unexpected side-products from indole addition to bulky cyclopropenes.

2.3.2 *Bis*-indolylalkanes

2.3.2.1 Reaction Optimisation

The optimisation for the 3-(*E*)-vinylindole products **123** was challenging due to their inseparability and instability. The *bis*-indolylalkanes **124**, however, do not suffer from these issues. These products are stable and purification is a much simpler task. The proposed mechanism of formation of products **124** is thought to proceed *via* the 3-(*E*)-vinylindoles; therefore if this is the case, the formation of the *bis*-indolylalkanes would require longer reaction times and higher temperatures (Table 2.7).

Table 2.7. Optimisation for formation of *bis*-indolylalkanes.



Entry	Catalyst	Equiv. Indole	Time (h)	Temperature (°C)	Ratio 124a:123a[a]	Yield 124a[b]
1	PPh_3AuNTf_2	1	7	20	>95:5	25%
2	**1**	2	18	20	46:54	35%
3	**1**	3	18	20	1:1	35%
4	**1**	2	18	reflux	90:10	63%
5	**1**	2.2	42	reflux	>99:1	76%

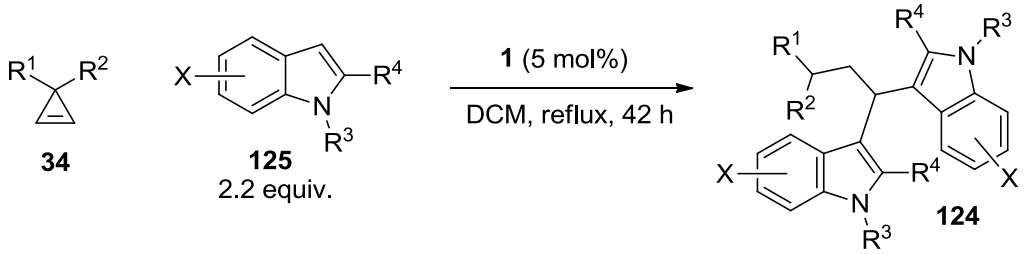
[a] Determined by ^{1}H NMR analysis of the crude mixture. [b] NMR yield by comparison with an internal standard (dimethyl sulfone).

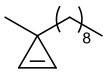
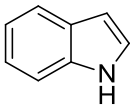
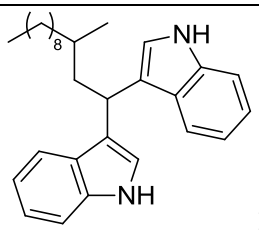
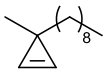
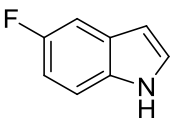
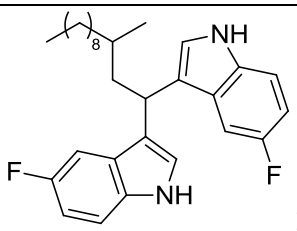
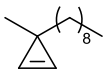
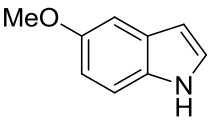
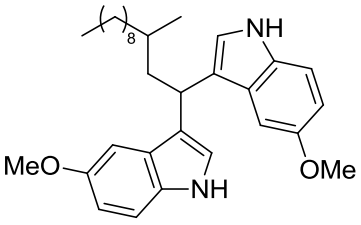
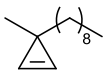
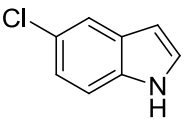
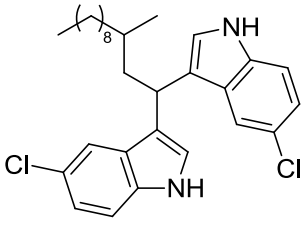
At lower temperatures (20 °C), the use of catalyst **1** gave a very poor ratio of products (close to 1:1), along with low yields (entries 2 & 3). The temperature of the reaction was increased to reflux (40 °C) and a vast improvement was observed (entries 4 & 5). The best conditions found were using **1**, 2.2 equivalents of indole and carrying out the reaction in refluxing DCM for 42 hours (entry 5). The 3-(*E*)-vinylindole product **123** was not observed in the ^{1}H NMR spectrum of the crude reaction mixture, and a good 76% yield of **124a** was attained.

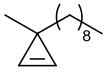
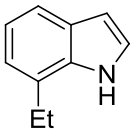
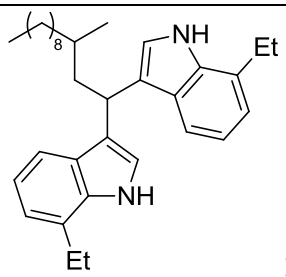
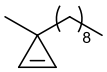
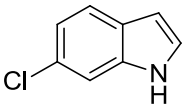
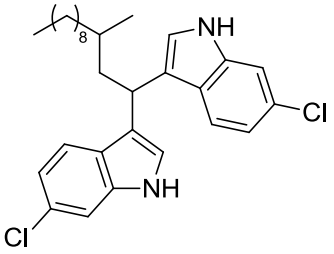
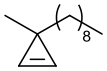
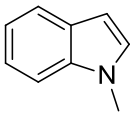
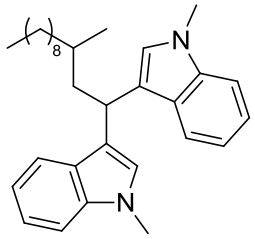
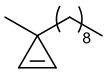
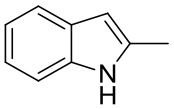
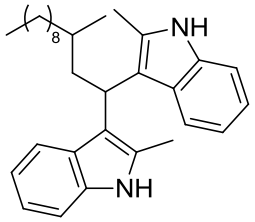
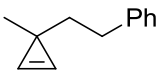
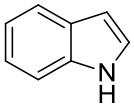
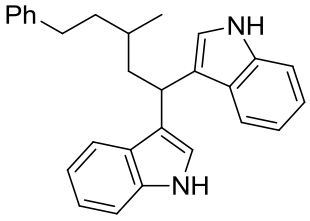
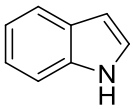
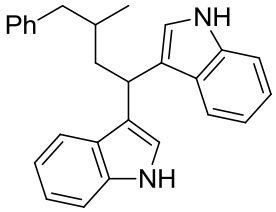
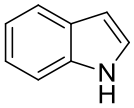
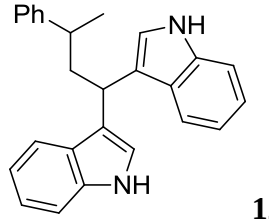
2.3.2.2 Reaction Scope

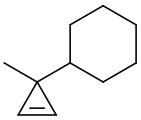
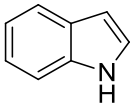
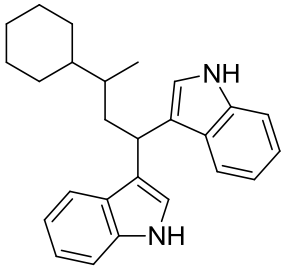
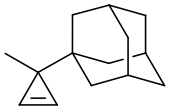
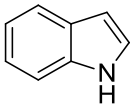
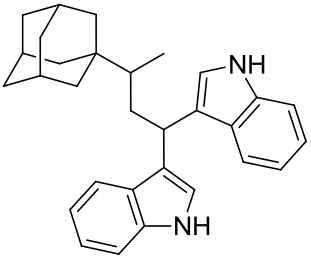
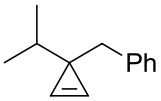
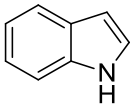
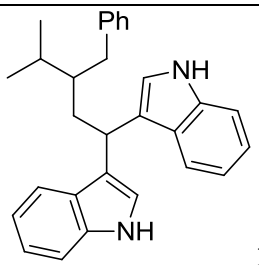
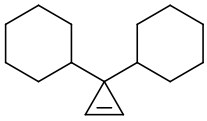
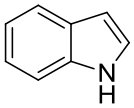
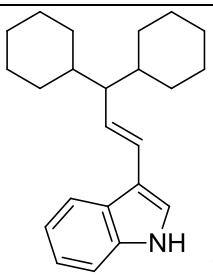
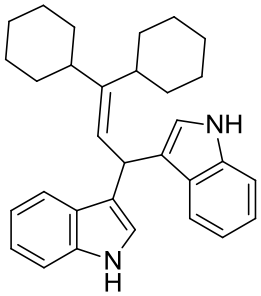
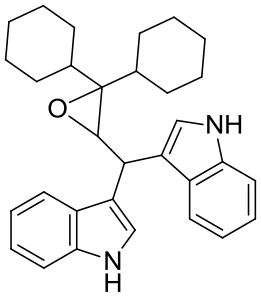
With the optimised conditions for the formation of **124** in hand, the same range of cyclopropenes **34** and indoles **125** were utilised again to ascertain the scope of this reaction (Table 2.8).

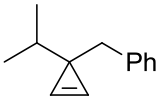
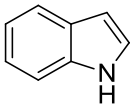
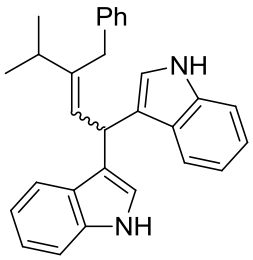
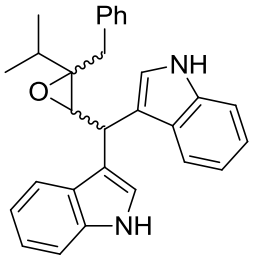
Table 2.8. Gold(I)-catalysed synthesis of *bis*-indolylalkanes.



Entry	21	Indole 3	Product	Yield[a]
1	 **34a**	 **125a**	 **124a**	69%
2	 **34a**	 **125b**	 **124b**	67%
3	 **34a**	 **125c**	 **124c**	60%
4	 **34a**	 **125d**	 **124d**	65%

5	 **34a**	 **125e**	 **124e**	48%
6	 **34a**	 **125f**	 **124f**	51%
7	 **34a**	 **125g**	 **124g**	71%
8	 **34a**	 **125h**	 **124h**	57%
9	 **34b**	 **125a**	 **124i**	69%
10	 **34c**	 **125a**	 **124j**	61%
11[b]	 **34d**	 **125a**	 **124k**	62%

12	 **34e**	 **125a**	 **124l**	56%
13	 **34f**	 **125a**	 **124m**	79%
14[c]	 **34g**	 **125a**	 **124n**	29%
15	 **34h**	 **125a**	 **123o**  **126b**  **127b**	0% **124o** 11% **123o** 35% **126b** 13% **127b**

16[e]	 **34g**	 **125a**	 **126a**  **127a**	0% **124n** 35% **126a** 34% **127a**

[a] Isolated yields. [b] 5 equiv. **125a** used. [c] Under N_2. [d] Products **123o** (11%), **126b** (35%) and **127b** (13%). [e] Under O_2, r.t., 24 h, **126a** (35%) and **127a** (34%).

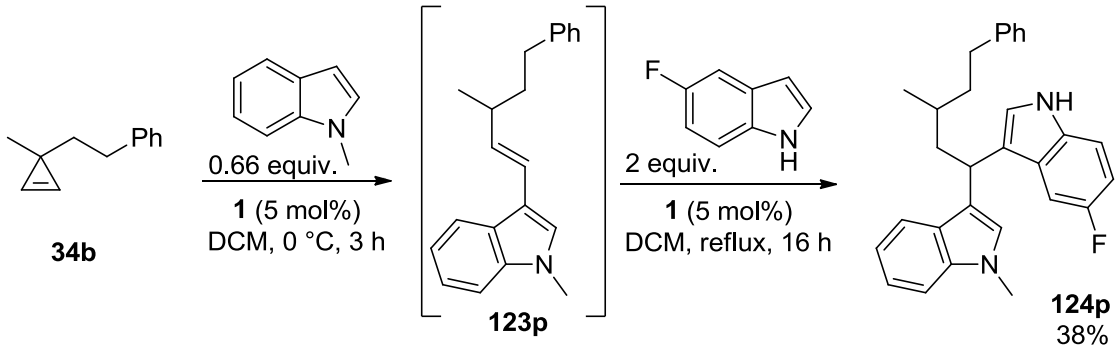
As with the 3-(*E*)-vinylindole products **123**, this reaction proceeds well with a number of cyclopropene **34** and indole **125** substrates. The yields are lower than that of the vinylindole products, however this could be attributed to the two-step reaction process; in which the vinylindole product **123** is formed, followed by reactivation of the alkene bond by gold(I) and nucleophilic addition of the second molecule of indole (see Section 2.3.4 for mechanistic studies).

Electron-rich and electron-poor indoles are all viable nucleophiles (entries 2-6). *N*-methylated and 2-methylindoles are also well tolerated in this reaction affording product **124** in 71% and 57% respectively (entries 7 & 8). A range of cyclopropenes were also found to react effectively in this reaction (entries 9-13), even when one substituent of the cyclopropene is sterically encumbered (entries 12 & 13).

As seen with the vinylindole scope (Table 2.6), when R^1 and R^2 on the cyclopropene substrate are bulky (**34g** and **34h**), a drastic change in reactivity occurs. Cyclopropene **34g** shows limited reactivity toward producing *bis*-indolylalkane **124n**. When the reaction is carried out under inert conditions (glovebox), a poor yield of 29% is achieved (entry 14). If this same reaction is performed under an oxygen atmosphere, the desired product **124n** is not observed. Instead, the unexpected oxidation products **126** and **127** are formed (entry 16). Since this reaction showed a drastic change in outcome from switching the reaction conditions from a nitrogen atmosphere to an oxygen atmosphere, it provides further evidence that there must be some form of oxidation

occurring for these products to appear. The use of cyclopropene **34h** in this reaction gave absolutely no desired *bis*-indolylalkane **124o** (entry 15). The vinylindole product **123o** was observed in 11% yield, along with **126b** and **127b** formed in 35% and 13% respectively. The unexpected oxidation products **126** and **127** will be discussed in more detail in section 2.3.3.

All products **124** obtained were symmetrical *bis*-indolylalkanes, however many of the naturally occurring structures are unsymmetrical *bis*-indolylalkanes. Therefore, a method for installing two different indoles into the structure would be desirable. A preliminary investigation showed that this could be achieved in a one-pot fashion by trapping the vinylindole product **123p** with an alternative indole to produce **124p** as a mixture of two diastereomers, in a 38% isolated yield over the two steps (Scheme 2.19).



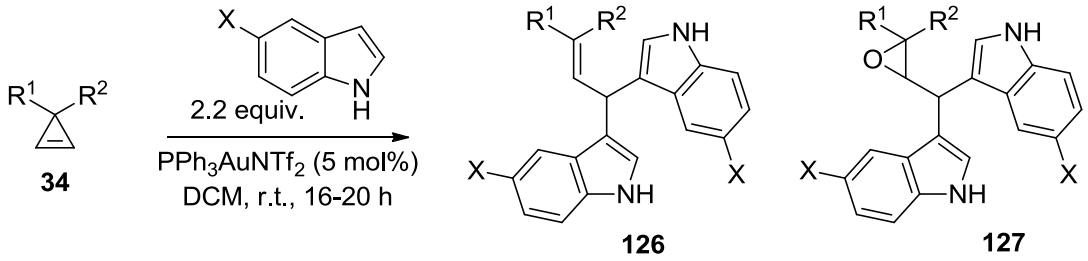
Scheme 2.19. One-pot synthesis of an unsymmetrical *bis*-indolylalkane.

The yield is low, however, this methodology is unoptimised. This reaction shows a proof-of-concept, and the reaction could be further developed to achieve better yields. Due to the conditions required to ensure full consumption of the *N*-methylindole in the first step (excess cyclopropene **34b**) and possible reversibility of **123** ⇌ **124** (see Section 2.3.4), there were three *bis*-indolylalkanes observed in the crude mixture. The three products were the desired product **124p**, and two symmetrical *bis*-indolylalkanes (6% and 11% by comparison to internal standard, but uncharacterised). This one-pot synthesis also provided further evidence that the *bis*-indolylalkane does indeed form *via* a 3-(*E*)-vinylindole intermediate.

2.3.3 Unexpected Oxidation Products

Throughout the investigations into the scope and generality of the two reactions discussed above (Table 2.6 & 2.8), there were surprising products obtained when the cyclopropene substrate contained two sterically bulky substituents (e.g. **34h**). The appearance of these unexpected products [*bis*-indolylalkene **126** and epoxide **127** (Figure 2.2)] led us to investigate these side-products in more detail.

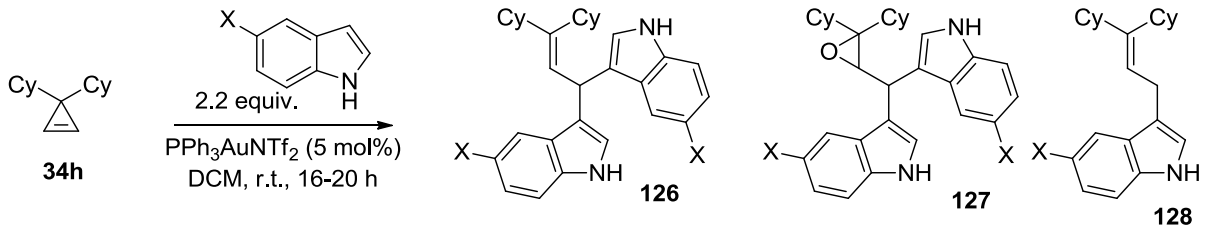
Two MChem project students in the Lee Group (K. Macleod and L. Arrowsmith) worked on optimising the conditions for producing oxidised products **126** and **127**, shown in Scheme 2.20. The choice of gold(I) catalyst changed to PPh_3AuNTf_2, and the reaction was left overnight at room temperature.



Scheme 2.20. Optimised conditions for the synthesis of unexpected oxidation products.

In order to explore this reaction further, a short study was carried out to explore various conditions of the reaction: varying from an inert environment to an oxygen atmosphere, and the effects of electron-withdrawing and electron-donating substituents on the indoles (Table 2.9).

Table 2.9. Gold(I)-catalysed indole additions to cyclopropene **34h**.

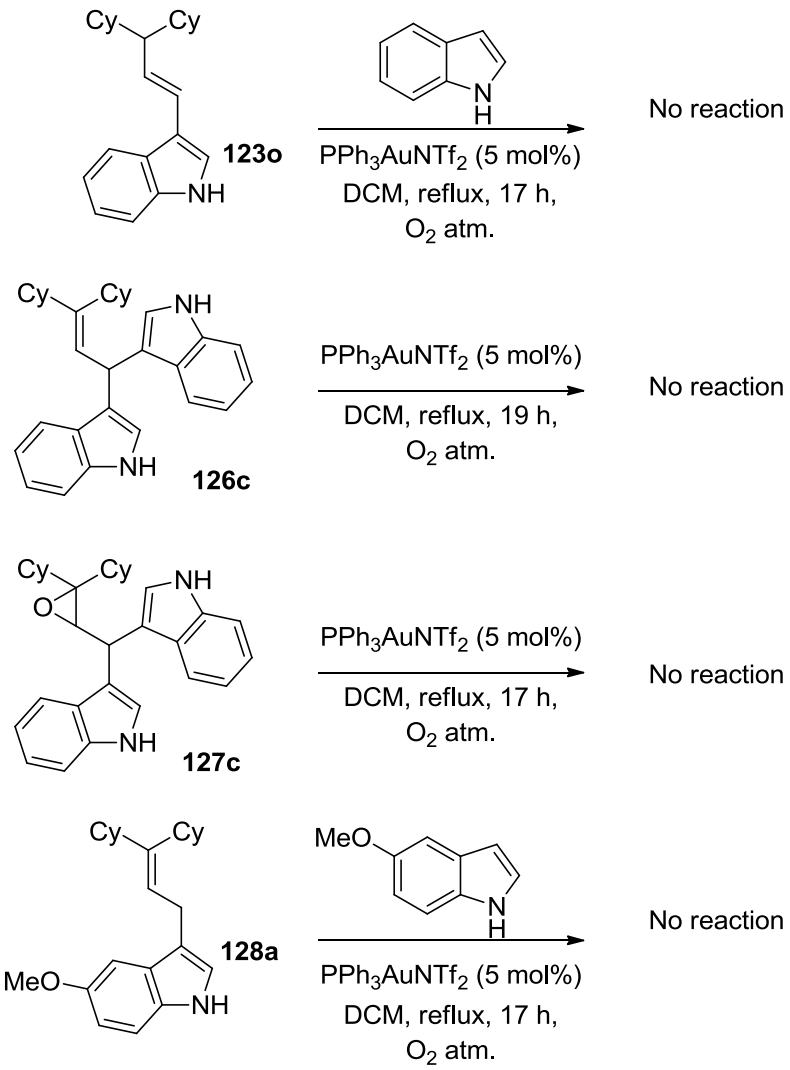


Entry[a]	**atm.**	**X**	**Yield 126**[b]	**Yield 127**[b]	**Yield 128**[c]
1	O_2	OMe	58% (50%)[c]	28% (27%)[c]	-
2	air	OMe	49%	16%	-
3	N_2[d]	OMe	-	-	44%
4	O_2	H	36% (34%)[c]	44% (28%)[c]	-
5	O_2	F	35% (34%)[c]	37% (34%)[c]	-

[a] No reaction occurs in the absence of Au(I) catalyst. [b] NMR yield by comparison to an internal standard. [c] Isolated yield. [d] In glovebox.

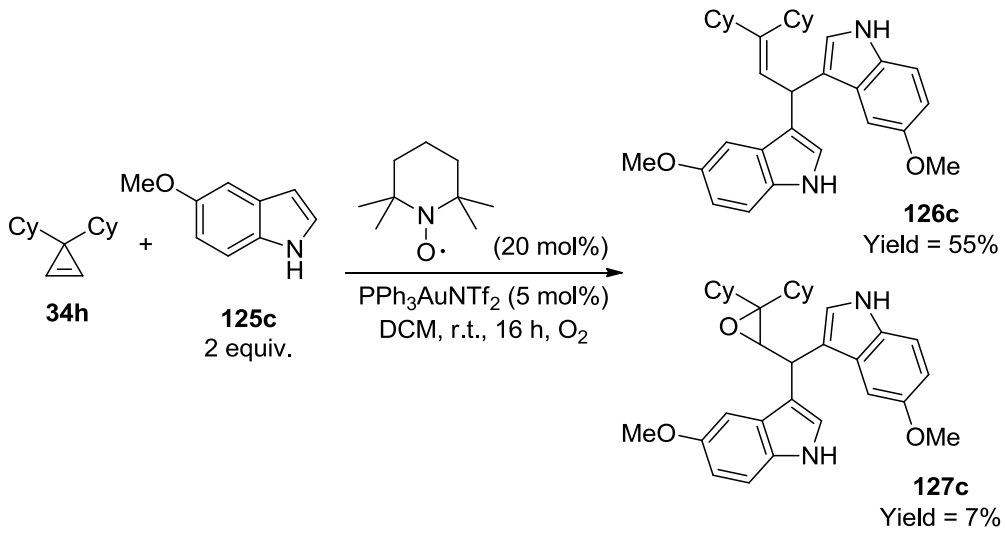
Varying the atmosphere of the reaction had a pronounced effect on the outcome (entries 1-3). Switching the conditions from air to an oxygen atmosphere improved the yields of both **126** and **127** (entry 2 *vs*. entry 1), demonstrating that oxygen aids the formation of these two products. Interestingly, if the reaction is carried out in the glovebox under a completely inert nitrogen atmosphere, products **126** and **127** are not observed. Instead, allylindole product **128a** is isolated from the reaction (entry 3). Allylindole product **128a** was never observed in any previous reactions, suggesting this product only forms in the complete absence of oxygen.

In an attempt to understand how these products are formed, several control reactions were carried out (Scheme 2.21). Products **123o**, **126c**, **127c** and **128a** were all resubjected to the reaction conditions shown in Scheme 2.20 under an oxygen atmosphere. Each control reaction showed only recovered starting materials, suggesting that the products are not formed from each other.



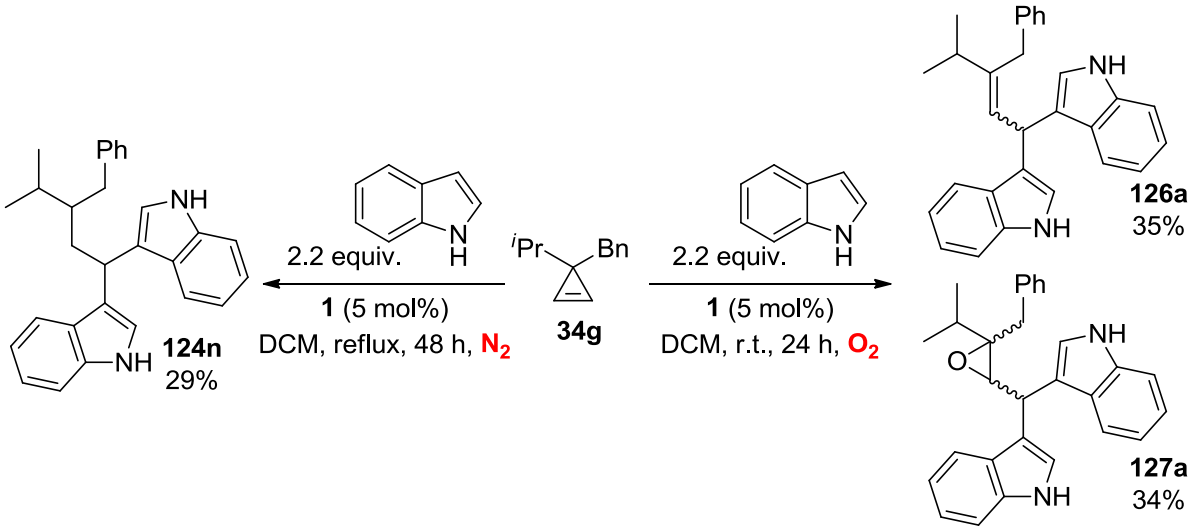
Scheme 2.21. Control reactions to determine potential oxidation mechanism.

A control reaction was performed with the radical scavenger TEMPO in the hope of gaining more insight into the formation of these oxidation products **126** and **127** (Scheme 2.22). *Bis*-indolylalkene **126c** was formed in 55% (NMR yield), which is comparable to the optimised reaction without TEMPO (58%, Table 2.9, entry 1). Conversely, a drastic decrease in yield is observed for epoxide **127c**, from 28% without TEMPO (Table 2.9, entry 1), down to 7% in the control reaction. Although not conclusive, this result suggests that the epoxide is formed *via* a radical pathway, whereas the *bis*-indolylalkene is not.



Scheme 2.22. Control reaction with radical scavenger TEMPO.

Products **126** and **127** are produced only when using cyclopropenes with bulky substituents. When cyclopropenes **34a-d** are used, products **126** and **127** are not observed. However, these products begin to be observed when cyclopropenes **34e** and **34f** are utilised, although these are in trace quantities (Table 2.6, entries 12-13). Selecting cyclopropene **34g** as the substrate results in a mixture of products, and the outcome can be controlled through using different reaction conditions (Scheme 2.23).

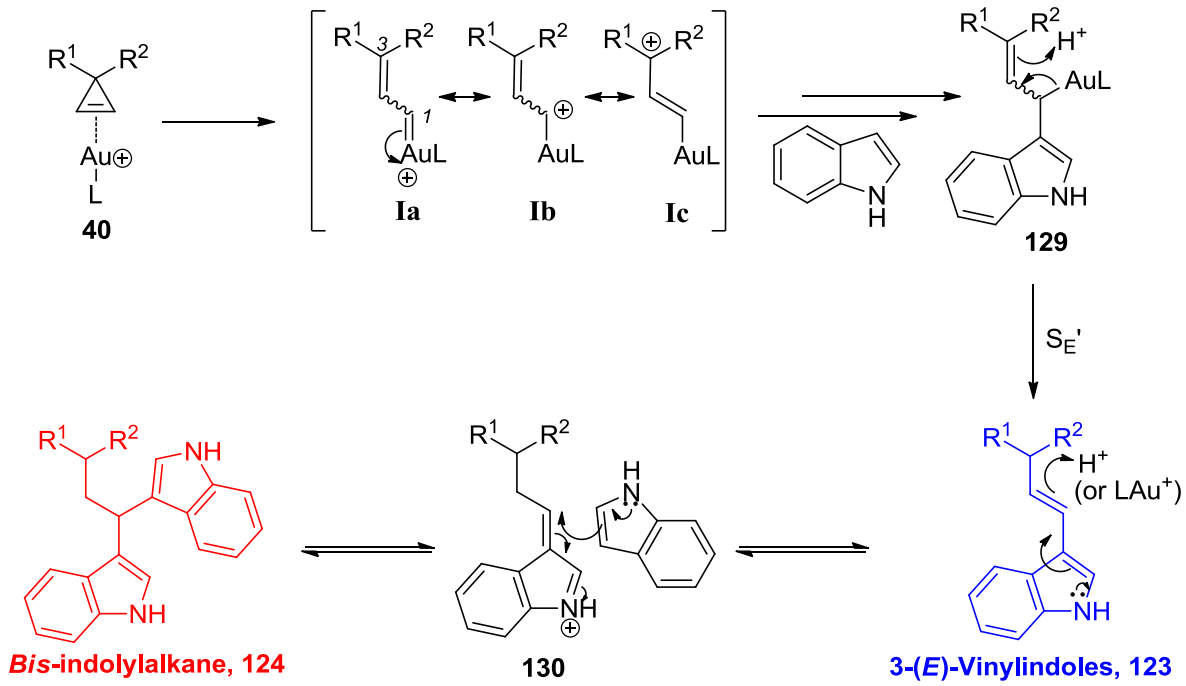


Scheme 2.23. Controlling reaction outcome by varying reaction atmosphere.

Under optimised reaction conditions for forming the *bis*-indolylalkane **124n** (from Table 2.8) with an inert nitrogen atmosphere, the desired product is afforded with a low 29% yield. Products **126a** and **127a** are not formed under these conditions. Altering the conditions slightly, with an oxygen atmosphere completely changes the outcome of the reaction. *Bis*-indolylalkane **124n** is *not* formed, however products **126a** and **127a** are obtained in 35% and 34% respectively; clearly showing that the formation of these two products require oxygen to form.

2.3.4 Mechanistic Studies

The results obtained throughout the investigations into the scope of the reaction allowed a proposed mechanism to be established (Scheme 2.24).

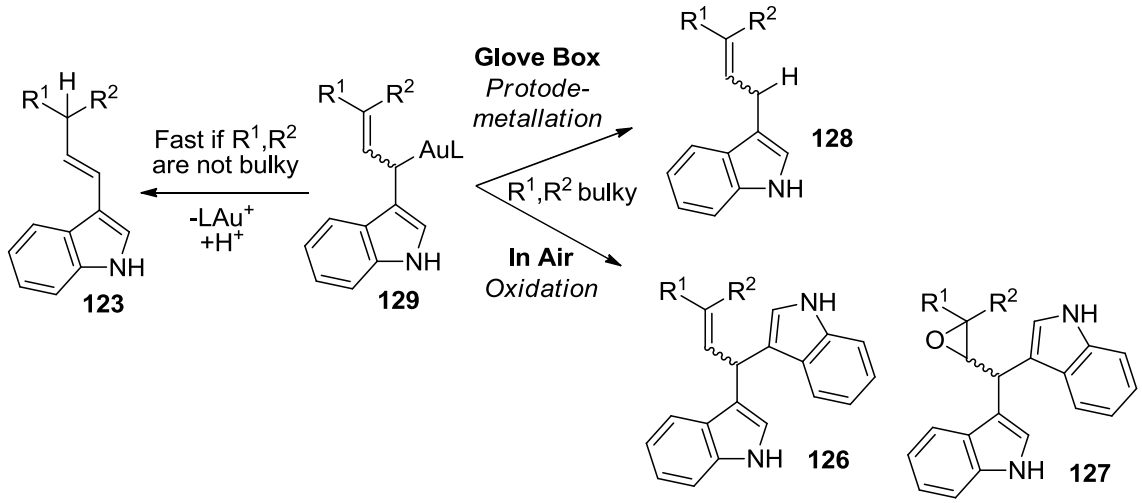


Scheme 2.24. Proposed mechanism for the gold(I)-catalysed addition of indole to cyclopropenes.

Gold(I) can selectively activate the cyclopropene alkene bond, which undergoes ring opening to intermediate **I**, which can be represented as three resonance forms, **Ia-c**.[42, 51] The indole nucleophile attacks at the C1 position, yielding intermediate **129**, which can undergo S_E' to release the desired 3-(*E*)-vinylindole product **123**. If given the opportunity, the double bond of product **123** may be activated by gold(I), or a Brønsted

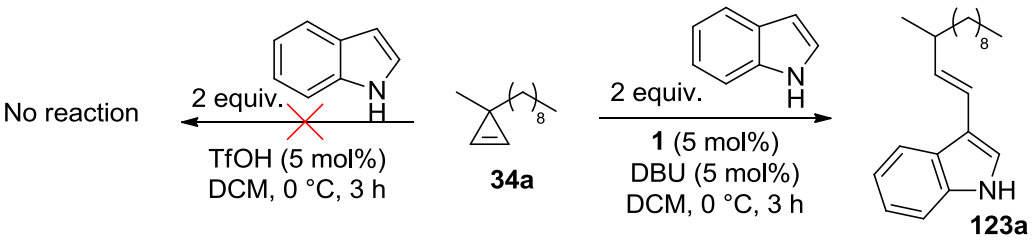
acid, to allow a second addition of indole (intermediate **130**) to obtain *bis*-indolylalkane product **124**. The formation of allylindole product **128**, acquired when bulky cyclopropenes are reacted under an inert nitrogen atmosphere, can be attributed to the direct protodemetallation of intermediate **129**.

The overall nature of intermediate **129** appears to be the most important factor in determining the outcome of the reaction. If R^1 and R^2 are not sterically encumbered, the S_E'step is fast, and 3-(*E*)-vinylindole **123** is produced. However, if R^1 and R^2 are bulky, intermediate **129** is reluctant to undergo S_E', and direct protodemetallation may occur in the absence of oxygen to afford allylindole **128**. In the presence of oxygen (or air), it is this intermediate **129** which undergoes oxidation to form *bis*-indolylalkene **126** and epoxide **127** (Scheme 2.25). However, the exact mechanism for this oxidation reaction is currently unclear.



Scheme 2.25. Proposed different outcomes from intermediate **129**.

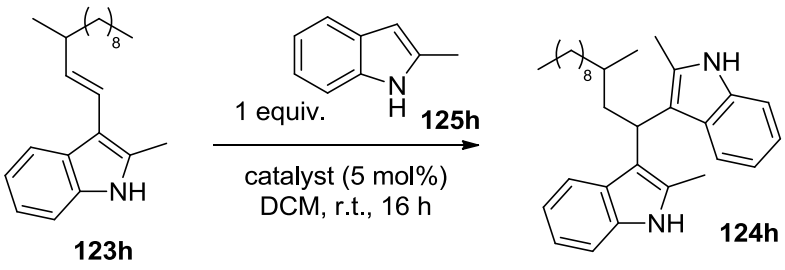
Next, to confirm that this reaction is indeed gold(I)-catalysed, control reactions were performed (Scheme 2.26). Cyclopropene **34a** still produced vinylindole **123a** with the addition of DBU (as a base to neutralise any trace acid), however under purely acid-catalysed conditions, no reaction took place. This implies that the formation of vinylindole products **123** requires the use of gold(I) catalysts.

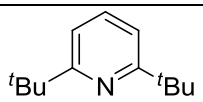


Scheme 2.26. Control reactions for vinylindole formation.

Several control reactions were carried out in an attempt to provide more evidence for the proposed mechanism for the formation of *bis*-indolylalkane **124** (Table 2.10). Vinylindole **123h** was isolated and resubjected to 2-methylindole (**125h**) and gold(I) catalyst **1**, full consumption of the vinylindole occurred and the *bis*-indolylalkane **124h** was observed in the ^{1}H NMR of the crude reaction mixture (entry 1). Addition of DBU (as a non-nucleophilic base to quench trace acid in the catalyst), showed only starting material vinylindole **123h** (entry 2). Utilising the extremely hindered base 2,6-di-*tert*-butylpyridine resulted in no reaction, with only vinylindole **123h** being recovered (entry 3). These results imply that the formation of the *bis*-indolylalkane **124** from vinylindole **123** is either acid-catalysed, or acid-assisted gold(I)-catalysis.[6]

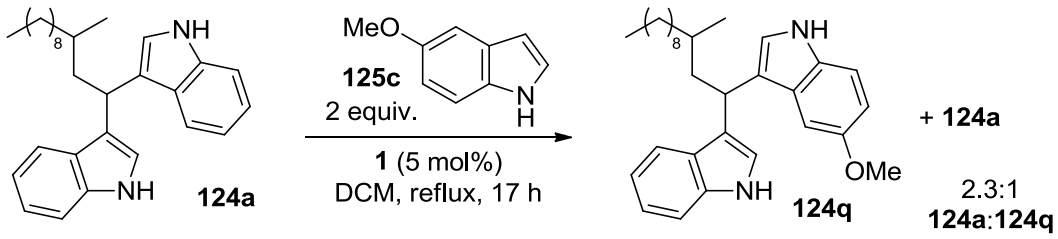
Table 2.10. Control reactions for *bis*-indolylalkane formation.



Entry	Catalyst	Base	Product[a]
1	**1**	-	**124h**
2	**1**	DBU (5 mol%)	**123h**
3	**1**	 (1 equiv.)	**123h**

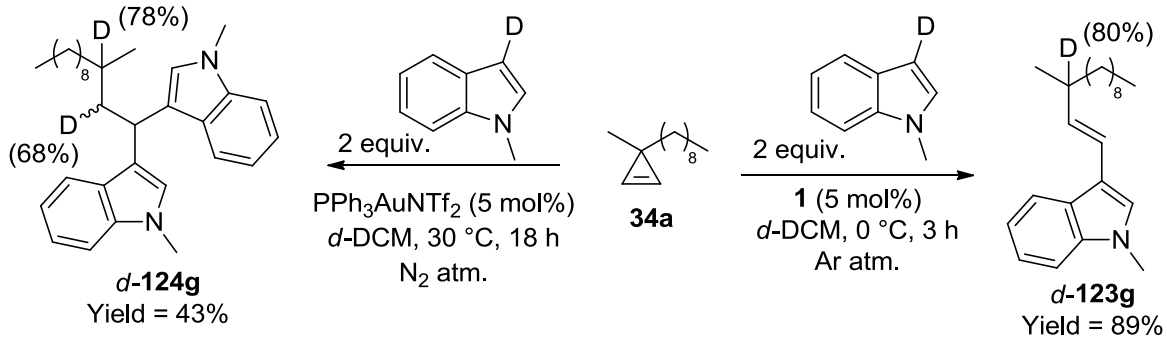
[a] By analysis of the ^{1}H NMR spectrum of crude reaction mixture.

Next, the reversibility of *bis*-indolylalkane formation was probed (Scheme 2.27).[6] *Bis*-indolylalkane **124a** was resubjected to the reaction conditions with a different indole substrate (5-methoxyindole **125c**). Analysis of the crude reaction mixture by ^{1}H NMR found that two *bis*-indolylalkane products were present (2.3:1 **124a**:**124q**). The reason for such behaviour could be attributed to the reversibility of **124a** and vinylindole **123a**, and further reaction of this vinylindole **123a** with 5-methoxyindole to give **124q**. This reaction provides evidence to conclude that the formation of *bis*-indolylalkane products are reversible, reverting back to their vinylindole intermediates (**123**).



Scheme 2.27. *Bis*-indolylalkane reversibility studies.

Further mechanistic evidence was gathered from a series of deuterium labelling studies (Scheme 2.28). *N*-methylindole was deuterated at the C3-position,[52] and reacted with cyclopropene **34a** under the standard optimised gold(I)-catalysed conditions. Carrying out the reaction to produce vinylindole *d*-**123g**, showed 80% deuterium incorporation solely at one position in the molecule, consistent with S_E' in Scheme 2.24 rather than protodemetallation followed by isomerisation. The corresponding reaction to obtain the *bis*-indolylalkane *d*-**124g** showed deuterium incorporation at the two expected positions after protodemetallation steps. These deuterium labelling studies provide good evidence for validating the proposed mechanism in Scheme 2.24.



Scheme 2.28. Deuterium labelling studies.

2.4 Conclusions & Future Work

A novel gold(I)-catalysed reaction of indole addition to cyclopropenes was developed. The reaction is *controllable*, so that specific products can be obtained depending on the reaction conditions utilised. For 3-(*E*)-vinylindole products **123**, useful as synthetic building blocks, a lower temperature and shorter reaction times are required. To achieve *bis*-indolylalkanes **124**, structures that can be found in natural products, the conditions are altered to higher temperatures and longer reaction times.

The scope of the reaction was investigated, and was found to be tolerant of many substitution patterns. The scope also showed that chloro-substituents on indole substrates are tolerated, which could be used as a handle for further functionalisation. Interestingly, when the steric bulk of the cyclopropene substituents are increased the product outcome alters dramatically. Instead of the expected products forming, unexpected oxidation products are observed; *bis*-indolylalkene **126** and epoxide **127**.

Currently the mechanism of formation of these two unexpected products remain unexplained, however it is known that they require a source of oxygen in order to form. In the absence of oxygen, allylindole **128** is afforded. A control reaction with radical scavenger TEMPO resulted in a decrease in yield of epoxide **127**, implying that this is potentially formed *via* a radical pathway. Future work in this area is required to fully understand the oxidation process and mechanism occurring in order to acquire these two surprising products.

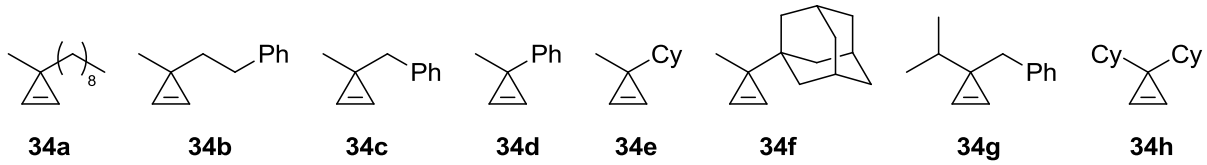
The mechanism of the controllable indole addition to cyclopropenes was probed through the use of deuterium labelling. The results harvested from this study provided agreeable evidence for the proposed mechanism (Scheme 2.24 *vide supra*).

2.5 Experimental

General Experimental Section

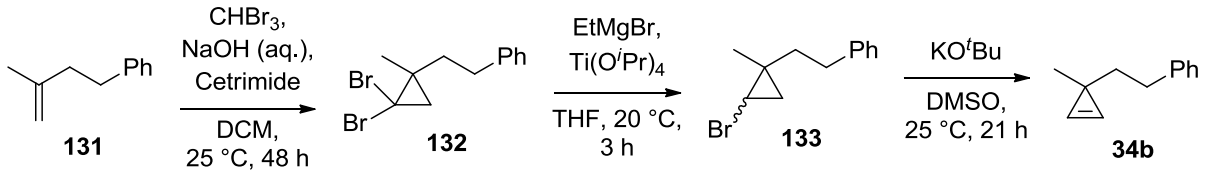
^{1}H NMR spectra were recorded on Bruker AC 200, AV 300 and AV 400 spectrometers at 200, 300 and 400 MHz respectively and referenced to residual solvent. ^{13}C NMR spectra were recorded using the same spectrometers at 50, 75 and 100 MHz respectively. Chemical shifts (δ in ppm) were referenced to tetramethylsilane (TMS) or to residual solvent peaks ($CDCl_3$ at δ_H 7.26). *J* values are given in Hz and s, d, dd, t, q, qn and m abbreviations correspond to singlet, doublet, doublet of doublet, triplet, quartet, quintet and multiplet. Mass spectra were obtained at the EPSRC National Mass Spectrometry Service Centre in Swansea. Infrared spectra were obtained on Perkin-Elmer Spectrum 100 FT-IR Universal ATR Sampling Accessory, deposited neat or as a chloroform solution to a diamond/ZnSe plate. Flash column chromatography was carried out using Matrix silica gel 60 from Fisher Chemicals and TLC was performed using Merck silica gel 60 F254 precoated sheets and visualised by UV (254 nm) or stained by the use of aqueous acidic $KMnO_4$ or aqueous acidic ceric ammonium molybdate as appropriate. Reactions were kept at 0 °C overnight using a jacketed reaction vessel attached to a Julabo FP40 Bohdan mini block temperature controlled recirculator with a Julabo temperature regulator. Petrol ether refers to petroleum ether (40–60 °C). Tetrahydrofuran was dried by distillation from sodium – benzophenone under nitrogen. Dimethylsulfoxide, acetonitrile and toluene were dried over calcium hydride. Dichloromethane (DCM) was purchased from Fisher and used without further purification. All indole substrates were purchased and used without further purification. The silver salts used were stored and weighed out in a glove box. The gold(I)-catalysed reactions were carried out without the need for dry solvents or inert atmosphere, unless otherwise stated.

Cyclopropene Substrate Synthesis



34a **34b** **34c** **34d** **34e** **34f** **34g** **34h**

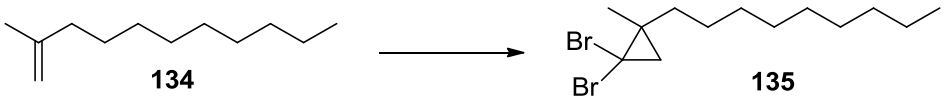
Cyclopropenes were synthesised following previously reported procedures, using a general procedure by Gevorgyan (Scheme 2.29).[51, 52] For example:



Scheme 2.29. General procedure for large scale synthesis of cyclopropenes by Gevorgyan.

Cyclopropene **34a**,[42] **34b** and **34d**[53, 54] were prepared by the author, and is described in the following experimental section. All other cyclopropene substrates were prepared by other members of the Lee Group, and available in the laboratory at the time of this study. The author thanks the following Lee Group members for the synthesis of cyclopropenes: **34c**[43] by Ursula Paul (Eramus project student), **34e** and **34f** by Richard Mudd (MChem project student), **34g** by Max Hadfield (PhD student) and **34h** by Lynn Arrowsmith (MChem project student) and Kristina Macleod (MChem project student).

1,1-Dibromo-2-methyl-2-nonylcyclopropane **135**:[42]

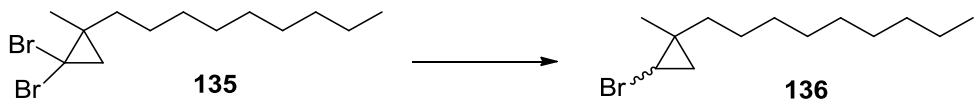


134 **135**

Bromoform (8.52 mL, 24.0 g, 95.0 mmol) and DCM (1.5 mL) were added dropwise over 30 min to a stirring mixture of aqueous sodium hydroxide (21 mL, 10 M), alkyltrimethylammonium bromide (1.94 g), 2-methylundec-1-ene **134** (8.0 g, 47.5 mmol) and DCM (10 mL). The mixture was allowed to stir vigorously at 35 °C. After 24 h, the reaction mixture was diluted with water (100 mL). Brine (500 mL) was added to aid separation of layers due to white emulsion forming. DCM (90 mL) was added and layers partitioned. The aqueous layer was washed twice with DCM (90 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting material was purified by flash column chromatography (petroleum ether 40-60 °C) and the remaining bromoform was evaporated under high vacuum (18 h, 30 °C) to the yield titled compound **135** (15.9 g, 46.7 mmol, 98%) as a colourless oil.

ν_{max}/cm^{-1} 2924 s 2854 m (C-H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72 – 1.44 (m, 4H, alkyl CH_2), 1.42 (d, *J* = 7.2 Hz, 1H, $CBr_2C\underline{H}H$), 1.39 (d, *J* = 7.2 Hz, 1H, $CBr_2CH\underline{H}$), 1.36 (s, 3H, $C(C\underline{H}_3)$), 1.27 (m, 12H, alkyl CH_2), 0.88 (t, *J* = 6.7, 3H, $CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.1 (C), 39.0 (CH_2), 35.0 (CH_2), 32.1(CH_2), 30.0 (C), 29.8 (CH_2), 29.74 (CH_2), 29.72 (CH_2), 29.5 (CH_2), 26.6 (CH_2), 22.8 (CH_2), 22.7 (CH_3), 14.3 (CH_3).

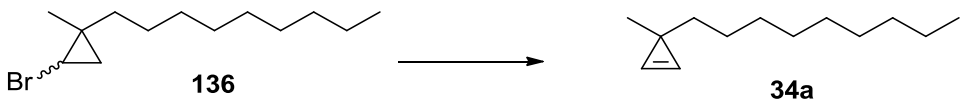
2-Bromo-1-methyl-1-nonylcyclopropane **136**:[42]



A solution of ethylmagnesium bromide (1.0 M in THF, 71 mL, 70.6 mmol) was added over 1.5 hours to a stirring solution of **135** (19.6 g, 57.6 mmol), $Ti(O^iPr)_4$ (1.78 mL, 1.67 g, 15.9 mmol) and THF (170 mL). The solution was allowed to stir for an additional 3 hours at r.t.. The reaction was quenched by slow addition of water (140 mL), then 20% aqueous sulfuric acid (150 mL) was added and the resulting mixture was stirred for 30 minutes. Diethyl ether (100 mL) was added and the layers were partitioned. The aqueous layer was washed a further two times with diethyl ether (100 mL). The combined organic layers were washed with saturated sodium bicarbonate (150 mL), washed with brine (150 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (pentane) to yield a mixture of the two diastereoisomers of the titled compound **136** (13.2 g, 50.5 mmol, 88%) as a colourless oil.

ν_{max}/cm^{-1} 2956 m 2924 s 2854 m (C-H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.82 (dd, *J* = 7.8, 4.2 Hz, 1H, C<u>H</u>BrCHH), 1.70 – 1.14 (m, 19H, alkyl CH_2 + CCH_3), 0.99 – 0.91 (m, 1H, C<u>H</u>HCHBr), 0.88 (t, *J* = 6.7 Hz, 3H, $CH_2C\underline{H_3}$), 0.67 – 0.57 (m, 1H, CH<u>H</u>CHBr); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.1 (CH_2), 39.0 (CH_2), 36.6 (CH_2), 32.08 (CH_2), 32.05 (CH_2), 30.8 (CH'), 30.3 (CH), 30.0 (CH_2), 29.83 (CH_2), 29.81 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.50 (CH_2), 29.48 (CH_2), 26.7 (CH_2), 26.6 (CH_2), 26.5 (CH_2), 23.0 (CH_2), 22.8 (CH_2), 22.6 (CH_2), 22.3 (CH_3'), 21.5 (C), 21.2 (C'), 20.4 (CH_3), 14.3 (CH_3), 14.2 (CH_3').

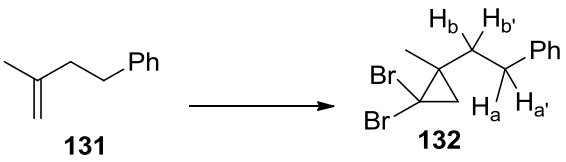
3-Methyl-3-nonylcycloprop-1-ene **34a**:[42]



Potassium *tert*-butoxide (8.90 g, 79.3 mmol) in DMSO (120 mL) was heated to 50 °C and allowed to stir for 30 minutes at this temperature. **136** (13.0 g, 49.8 mmol) was added dropwise over 1.5 hours. The reaction mixture was allowed to stir for 17.5 hours at 50 °C, and then cooled before it was quenched by addition of water (250 mL). Pentane (100 mL) was added and the layers partitioned. The aqueous layer was washed three times with pentane (100 mL). The combined organic layers were washed three times with brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting material was purified by flash column chromatography (pentane) to yield the titled compound **34a** (7.29 g, 40.4 mmol, 81 %) as a colourless oil.

ν_{max}/cm^{-1} 1959 w 2922 s 2853 m (C-H), 1628 w (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.35 (q, *J* = 0.7 Hz, 2H, C<u>H</u>=C<u>H</u>), 1.49 – 1.17 (m, 16H, alkyl CH_2), 1.14 (t, *J* = 0.7 Hz, 3H, C(C<u>H</u>$_3$)), 0.88 (t, *J* = 6.7 Hz, 3H, CH_2C<u>H</u>$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 122.3 (CH), 40.4 (CH_2), 32.1 (CH_2), 30.0 (CH_2), 29.8 (CH_2), 29.6 (CH_2 overlapping peaks), 27.5 (CH_3), 27.3 (CH_2), 22.9 (CH_2), 20.3 (C), 14.3 (CH_3).

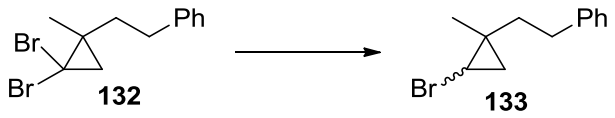
(2-(2,2-Dibromo-1-methylcyclopropyl)ethyl)benzene **132**:



Bromoform (41.5 g, 164 mmol) and DCM (5 mL) were added dropwise over 2 hours to a stirring mixture of aqueous sodium hydroxide (38 mL, 10 M), alkyltrimethylammonium bromide (3.50 g), 4-phenyl-2-methyl-but-1-ene **131** (12.0 g, 82.1 mmol) and DCM (15 mL). The mixture was allowed to stir vigorously at 25 °C. After 48 h, the reaction mixture was diluted with water (150 mL). DCM (50 mL) was added and layers partitioned. The aqueous layer was washed twice with DCM (50 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting material was purified by flash column chromatography (pentane) and the remaining bromoform was evaporated under high vacuum (18 h, 30 °C) to yield the titled compound **132** (21.0 g, 66.1 mmol, 81 %) as a colourless oil.

ν_{max}/cm^{-1} 3026 w 2958 w 2928 w 2861 w (C-H), 1495 m 1454 m 1428 w 1381 w (Aromatic C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.15 (m, 5H, Ar-H), 2.91 (ddd, *J* = 13.4, 11.9, 4.7 Hz, 1H, C$\underline{H}_{2a/a'}$Ph), 2.77 (ddd, *J* = 13.4, 11.9, 5.6 Hz, 1H, C$\underline{H}_{2a/a'}$Ph), 2.03 (ddd, *J* = 13.9, 11.9, 5.6 Hz, 1H, C$\underline{H}_{2b/b'}$$CH_2$Ph), 1.88 (ddd, *J* = 13.9, 11.9, 4.7 Hz, 1H, C$\underline{H}_{2b/b'}$$CH_2$Ph), 1.48 (s, 3H, CH_3), 1.45 (app. d, *J* = 1.1 Hz, 2H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.9 (C), 128.6 (CH), 128.4 (CH), 126.1 (CH), 41.3 (CH_2), 39.2 (C), 35.1 (CH_2), 32.9 (CH_2), 29.7 (C), 22.8 (CH_3); Found (EI) $[M]^+$ 315.9458, $C_{12}H_{14}Br_2$ requires 315.9457.

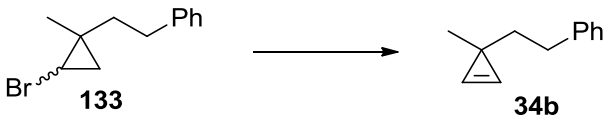
(2-(2-Bromo-1-methylcyclopropyl)ethyl)benzene **133**:



A solution of ethylmagnesium bromide (2.83 M in THF, 7.93 mL, 18.9 mmol) was added over 1 hour to a stirring solution of **132** (12.0 g, 37.7 mmol), $Ti(O^iPr)_4$ (0.54 g, 1.89 mmol) and THF (75 mL). The solution was allowed to stir for an additional 3 hours at r.t.. The reaction was quenched by slow addition of water (25 mL), then 20% aqueous sulfuric acid (50 mL) was added and the resulting mixture was stirred for 30 minutes. Diethyl ether (50 mL) was added and the layers were partitioned. The aqueous layer was washed a further three times with diethyl ether (50 mL). The combined organic layers were washed with saturated sodium bicarbonate (50 mL), washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (pentane) to yield a mixture of the two diastereoisomers of the titled compound **133** (3.37 g, 14.1 mmol, 37%) as a colourless oil.

ν_{max}/cm^{-1} 3027 m 2926 m 2859 m (C-H), 1604 m 1496 m 1454 s (Ar C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.17 (m, 5H + 5H', Ar-H + Ar-H'), 3.00 – 2.82 (m, 1H + 2H', C<u>H</u>Br + C<u>H</u>Br' + C<u>H</u>HPh'), 2.82 – 2.69 (m, 2H + 1H', C<u>H</u>$_2$Ph + CH<u>H</u>Ph'), 1.96 (ddd, *J* = 13.9, 11.8, 5.7 Hz, 1H', C<u>H</u>HCH$_2$Ph'), 1.85 (ddd, *J* = 13.9, 11.7, 4.8 Hz, 1H', CH<u>H</u>CH$_2$Ph'), 1.76 – 1.52 (m, 2H, C<u>H</u>$_2$CH$_2$Ph), 1.39 (s, 3H, CH_3), 1.23 (s, 3H', CH_3'), 1.05 (app. dd, *J* = 7.5, 6.4 Hz, 1H + 1H', C<u>H</u>HCHBr, C<u>H</u>HCHBr'), 0.80 – 0.66 (m, 1H + 1H', CH<u>H</u>CHBr, CH<u>H</u>CHBr'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.5 (C), 142.1 (C), 128.5 (CH), 128.5 (CH), 128.5 (CH), 128.4 (CH), 126.0 (CH), 125.9 (CH), 41.2 (CH_2), 39.0 (CH_2), 33.0 (CH_2), 32.9 (CH_2), 30.3 (CH), 29.9 (CH), 23.1 (CH_2), 22.7 (CH_2), 22.2 (CH_3), 21.4 (C), 21.0 (C), 20.4 (CH_3); Found (APCI) $[M+H]^+$ 239.0430, $C_{12}H_{16}Br$ requires 239.0430.

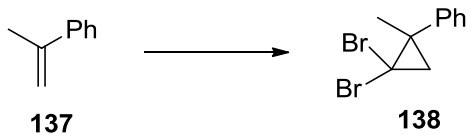
2-(1-Methylcycloprop-2-en-1-yl)ethyl)benzene **34b**:



Potassium *tert*-butoxide (2.25 g, 20.1 mmol) in DMSO (20 mL) was heated to 55 °C and allowed to stir for 30 minutes at this temperature. The solution was cooled to room temperature and **133** (3.22 g, 13.5 mmol) was added dropwise over 3 hours. The reaction mixture was allowed to stir for 21 h at r.t., and then quenched by addition of water (100 mL). Pentane (400 mL) was added and the layers partitioned. The aqueous layer was washed three times with pentane (50 mL). The combined organic layers were washed twice with brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting material was purified by flash column chromatography (pentane) to yield the titled compound **34b** (1.15 g, 7.26 mmol, 58%) as a colourless oil.

ν_{max}/cm^{-1} 3063 w 3027 w 2962 w 2854 m 2854 m (C-H), 1628 m (alkene C=C) 1584 w 1497 m 1453 m (aromatic C=C) ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.31 (app. sextet, J = 0.7 Hz, 2H, alkene-H), 7.30 – 7.14 (m, 5H, Ar-H), 2.51 – 2.40 (m, 2H, $CH_2C\underline{H_2}Ph$), 1.86 – 1.75 (m, 2H, $C\underline{H_2}CH_2Ph$), 1.20 (t, J = 0.7 Hz, 3H, $C\underline{H_3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.2 (C), 128.5 (CH), 128.3 (CH), 125.6 (CH), 122.0 (CH), 42.1 (CH_2), 33.6 (CH_2), 27.3 (CH_3), 20.2 (C); Found (EI) $[M-H]^+$ 157.1011, $C_{12}H_{13}$ requires 157.1012.

(2,2-Dibromo-1-methylcyclopropyl)benzene **138**:[53, 54]

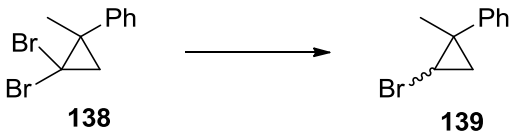


137 **138**

Bromoform (15.2 mL, 169 mmol) dissolved in DCM (5 mL) were added dropwise over 2 hours to a stirring mixture of aqueous sodium hydroxide (37 mL, 10 M), alkyltrimethylammonium bromide (3.4 g), α-methylstyrene **137** (10.2 g, 86 mmol) and DCM (15 mL). The mixture was allowed to stir vigorously at 25 °C. After 48 h, the reaction mixture was diluted with water (150 mL). DCM (50 mL) was added and layers partitioned. The aqueous layer was washed twice with DCM (50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting material was purified by flash column chromatography (pentane) and the remaining bromoform was evaporated under high vacuum (18 h, 50 °C) to yield the titled compound **138** (21.5 g, 74 mmol, 86 %) as a colourless oil.

ν_{max}/cm^{-1} 2981 m 2959 w 2924 w (C-H), 1424 m 1444 m 1600 w (C=C aromatic); ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.25 (m, 5H, Ar-H), 2.18 (d, *J* = 7.6 Hz, 1H, CH<u>H</u>), 1.79 (d, *J* = 7.6 Hz, 1H, C<u>H</u>H), 1.73 (s, 3H, CC<u>H</u>$_3$); ^{13}C NMR (50 MHz, $CHCl_3$) δ 142.6 (C), 128.7 (CH), 128.7 (CH), 127.5 (CH), 37.1 (C), 36.0 (C), 34.0 (CH_2), 28.1 (CH_3).

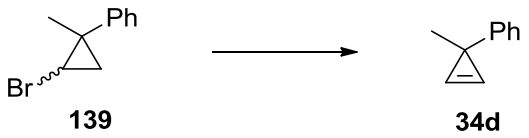
(2-Bromo-1-methylcyclopropyl)benzene **139**:[53, 54]



A solution of ethylmagnesium bromide (1.9 M in THF, 40 mL, 76 mmol) was added over 1 hour to a stirring solution of **138** (20.0 g, 69 mmol), $Ti(O^iPr)_4$ (2.05 mL, 6.90 mmol) and THF (140 mL). The solution was allowed to stir for an additional 3 hours at room temperature. The reaction was quenched by slow addition of water (40 mL), then 20% aqueous sulfuric acid (80 mL) was added and the resulting mixture was stirred for 30 minutes. Diethyl ether (60 mL) was added and the layers were partitioned. The aqueous layer was washed a further two times with diethyl ether (60 mL). The combined organic layers were washed with saturated sodium bicarbonate (60 mL), washed with brine (60 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (pentane) to yield a mixture of the two diastereoisomers of the titled compound **139** (3.37 g, 14.1 mmol, 37 %) as a colourless oil.

ν_{max}/cm^{-1} 3083 w 3059 w 2981 m 2959 w 2924 w (C-H), 1600 m 1496 m 1444 m (aromatic ring vibrations); ^1H NMR (200 MHz, $CDCl_3$) δ 7.36 – 7.15 (m, 5H, Ar-H), 3.22 (dd, *J* = 8.1, 4.7 Hz, 1H, CHHC<u>H</u>Br), 1.64 (s, 4H, C(C<u>H</u>$_3$) + C<u>H</u>HCHBr), 1.07 (dd, *J* = 6.5, 4.7 Hz, CH<u>H</u>CHBr); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 144.6 (C), 142.3 (C), 129.6 (CH), 128.7 (CH), 128.3 (CH), 127.1 (CH), 126.9 (CH), 126.7 (CH), 30.7 (CH), 28.4 (CH_3), 27.7 (C), 27.1 (CH), 25.9 (C), 24.1 (CH_3), 23.5 (CH_2), 22.2 (CH_2).

(1-Methylcycloprop-2-en-1-yl)benzene **34d**:[53, 54]



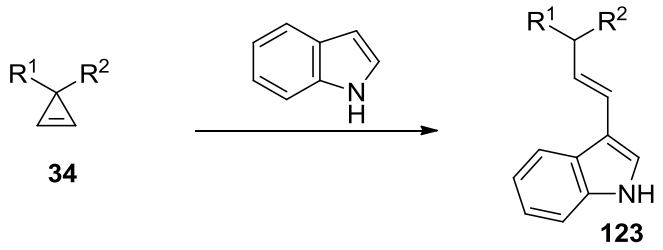
139 **34d**

Potassium *tert*-butoxide (1.69 g, 15.2 mmol) was dissolved in DMSO (20 mL). **139** (2.00 g, 9.47 mmol) was added dropwise over 1 hour. The reaction mixture was allowed to stir overnight at r.t., and then quenched by addition of water (100 mL). Pentane (100 mL) was added and the layers partitioned. The aqueous layer was washed three times with pentane (100 mL). The combined organic layers were washed twice with brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting material was purified by flash column chromatography (pentane) to yield the titled compound **34d** (0.40 g, 3.07 mmol, 33%) as a colourless oil.

ν_{max}/cm^{-1} 2969 m (C-H), 1638 m (alkene C=C), 1578 m 1492 m 1444 m (aromatic ring vibrations); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33 – 7.14 (m, 7H, Ar-H + C<u>H</u>=C<u>H</u>), 1.64 (t, *J* = 0.6 Hz, C(C<u>H</u>$_3$)); ^{13}C NMR (50 MHz, $CHCl_3$) δ 150.1 (C), 127.9 (CH), 126.2 (CH), 125.1 (CH), 115.6 (CH), 25.5 (CH_3), 21.9 (C).

General procedure for 3-vinylindole formation:

3-(*E*)-Vinylindole **123** general synthetic procedure (NMR Yields, Procedure A):

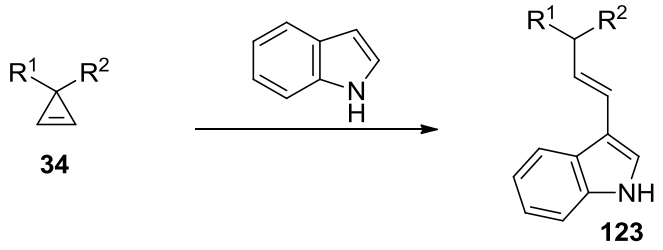


To a solution of cyclopropene (1 equiv.)[‡] and indole (2 equiv.) in DCM (0.139 M), 5 mol% of catalyst **1** was added. The solution was allowed to stir for 3 h at 0 °C. The reaction was filtered through a silica plug, washed with diethyl ether and 2% triethylamine. The filtrate was concentrated under reduced pressure and a ^{1}H-NMR spectrum in $CDCl_3$ was obtained of the crude mixture, using a known amount of dimethyl sulfone as an internal standard.

Note: *Alkyl* substituted 3-vinylindoles are known to have limited stability and will decompose readily.[5] Repeated attempts at silica, triethylamine buffered silica, alumina and florisil chromatography all resulted in partial decomposition and any isolated vinylindoles **123** would begin to decompose within <1 day. In order to access enough isolated pure material for full characterisation of these novel vinylindoles **123**, the procedure B shown below was used as the product can be isolated using a very quick and short plug of silica. Although decomposition still occurs, this method provides enough clean material for immediate full characterisation of the new alkyl vinylindoles **123**.

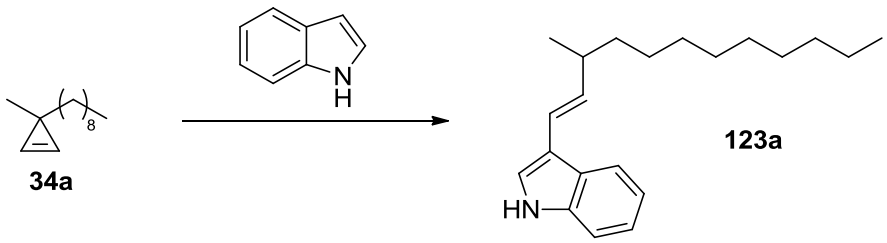
[‡] All reactions were performed on 15 mg scale.

3-(*E*)-Vinylindole **123** general synthetic procedure (For Isolation and characterisation, Procedure B):



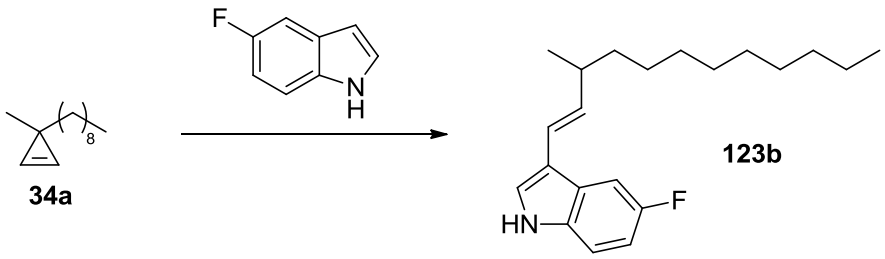
To a solution of cyclopropene (1 equiv.) and indole (0.66 equiv.) in DCM (0.139 M), 5 mol% of catalyst **1** was added. The solution was allowed to stir for 4.5 h at room temperature. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (very short silica column to minimise decomposition).

(E)-3-(3-Methyldodec-1-enyl)-1H-indole **123a:**



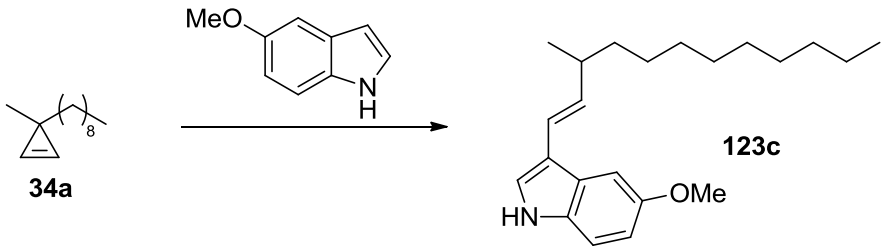
Procedure A: Using **34a** (15.2 mg, 0.084 mmol) to yield 91% of **123a** by ^{1}H NMR analysis. Procedure B: Using **34a** (15.2 mg, 0.084 mmol) to yield **123a** (5.5 mg, 0.018 mmol, 34%). Purified using an eluent system of neat hexane → 5:1 hexane:diethyl ether. R_f 0.20 (5:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3411 w (N-H), 2923 s 2849 m (C-H), 1622 w (C=C), 1581 w 1509 w 1482 s (Ar C=C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H, N<u>H</u>), 7.87 (d, *J* = 7.9 Hz, 1H, Ar-H), 7.36 (dd, *J* = 6.9, 1.2 Hz, 1H, Ar-H), 7.25 – 7.12 (m, 3H, Ar-H), 6.52 (d, *J* = 16.1 Hz, 1H, CH=C<u>H</u>C), 6.08 (dd, *J* = 16.1, 7.9 Hz, 1H, CHC<u>H</u>=CH), 2.29 (m, 1H, $CH_3C\underline{H}CH_2$), 1.49 – 1.16 (m, 16H, alkyl CH_2), 1.11 (d, *J* = 6.7 Hz, 3H, $CHC\underline{H_3}$), 0.87 (t, *J* = 6.7 Hz, 3H, $CH_2C\underline{H_3}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.9 (C), 134.7 (CH), 125.9 (C), 122.5 (CH), 122.2 (CH), 120.3 (CH), 120.2 (CH), 120.1 (CH), 115.9 (C), 111.3 (CH), 38.0 (CH), 37.7 (CH_2), 32.1 (CH_2), 30.0 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 27.7 (CH_2), 22.9 (CH_2), 21.2 (CH_3), 14.3 (CH_3). Found (ESI) $[M+H]^+$ 298.2526, $C_{21}H_{32}N$ requires 298.2529.

(*E*)-5-Fluoro-3-(3-methyldodec-1-en-1-yl)-1H-indole **123b**:



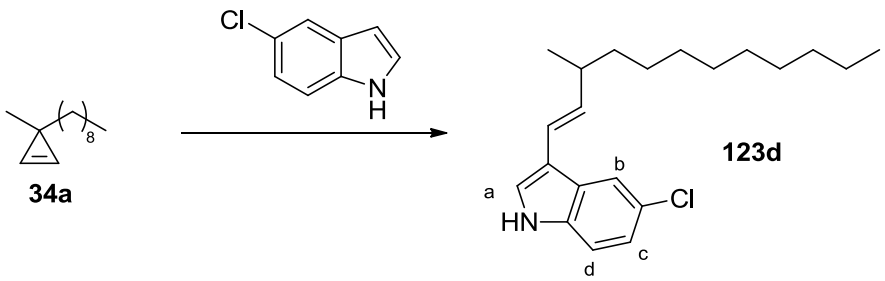
Procedure A: Using **34a** (15.1 mg, 0.084 mmol) to yield 72% of **123b** by ^{1}H NMR analysis. Procedure B: Using **34a** (20.6 mg, 0.114 mmol) to yield **123b** (34.2 mg, 0.076 mmol, 67%). Purified using an eluent system of 7:1 hexane:diethyl ether. R_f 0.13 (5:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3421 w (N-H) 2959 m 2924 s 2854 m (C-H), 1656 w (C=C) 1628 w 1580 w (Ar C=C), 1094 s (C-F); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 1H, NH), 7.42 (dd, *J* = 10.0, 2.5 Hz, 1H, Ar-H), 7.22 – 7.13 (m, 2H, Ar-H), 6.88 (td, *J* = 9.0, 2.5 Hz, 1H, Ar-H), 6.38 (d, *J* = 16.1 Hz, 1H, CHCH=C<u>H</u>), 5.93 (dd, *J* = 16.1, 7.9 Hz, 1H, CHC<u>H</u>=CH), 2.21 (m, 1H, $CH_3C\underline{H}$), 1.45 – 1.07 (m, 16H, alkyl CH_2), 1.03 (d, *J* = 6.7 Hz, 3H, CHC<u>H</u>$_3$), 0.80 (t, *J* = 6.7 Hz, 3H, $CH_2C\underline{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7 (C), 134.9 (CH), 133.3 (C), 126.2 (d, *J* = 9.6 Hz, C), 123.9 (CH), 119.9 (CH), 116.0 (d, *J* = 4.6 Hz, C) 111.9 (d, *J* = 9.8 Hz, CH), 110.8 (d, *J* = 26.5 Hz, CH), 105.3 (d, *J* = 24.5 Hz, CH), 38.0 (CH), 37.6 (CH_2), 32.1 (CH_2), 30.0 (CH_2), 29.8 (2 × CH_2), 29.5 (CH_2), 27.7 (CH_2), 22.9 (CH_2), 21.2 (CH_3), 14.3 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ -124.2 (td, *J* = 9.6, 4.4 Hz). Found (APCI) $[M+H]^+$ 316.2437, $C_{21}H_{31}FN$ requires 316.2435.

(*E*)-5-Methoxy-3-(3-methyldodec-1-en-1-yl)-1H-indole **123c:**



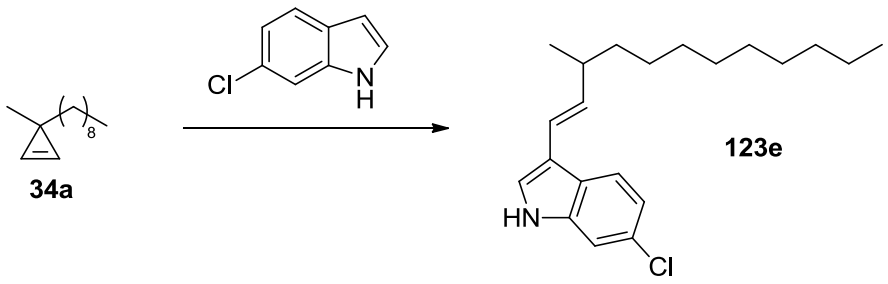
Procedure A: Using **34a** (15.5 mg, 0.086 mmol) to yield 65% of **123c** by ^{1}H NMR analysis. Procedure B: Using **34a** (14.9 mg, 0.088 mmol) to yield **123c** (8.5 mg, 0.026 mmol, 45%). Purified using an eluent system of 6:1 hexane:diethyl ether. R_f 0.17 (5:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3410 m (N-H), 2955 s 2923 s 2853 s (C-H), 1654 w (C=C), 1624 m 1582 m (Ar C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (s, 1H, N<u>H</u>), 7.29 (d, *J* = 2.4 Hz, 1H, Ar-H), 7.25 (d, *J* = 8.8 Hz, 1H, Ar-H), 7.17 (d, *J* = 2.6 Hz, 1H, Ar-H), 6.88 (dd, *J* = 8.8, 2.4 Hz, 1H, Ar-H), 6.49 (d, *J* = 16.1 Hz, 1H, CHCH=C<u>H</u>), 6.01 (dd, *J* = 16.1, 7.9 Hz, 1H, CHC<u>H</u>=CH), 3.89 (s, 3H, OC<u>H</u>$_3$), 2.29 (m, 1H, CH_3C<u>H</u>), 1.51 – 1.17 (m, 16H, alkyl CH_2), 1.11 (d, *J* = 6.7 Hz, 3H, CHC<u>H</u>$_3$), 0.87 (t, *J* = 6.7 Hz, 3H, CH_2C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5 (C), 134.2 (CH), 132.0 (C), 126.3 (C), 122.9 (CH), 120.2 (CH), 115.6 (C), 112.3 (CH), 111.9 (CH), 102.5 (CH), 56.2 (CH_3), 37.9 (CH), 37.7 (CH_2), 32.1 (CH_2), 30.0 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 27.7 (CH_2), 22.9 (CH_3), 21.2 (CH_2), 14.3 (CH_3). Found (APCI) $[M+H]^+$ 328.2636, $C_{22}H_{34}NO$ requires 328.2635.

(*E*)-5-Chloro-3-(3-methyldodec-1-en-1-yl)-1H-indole **123d**:



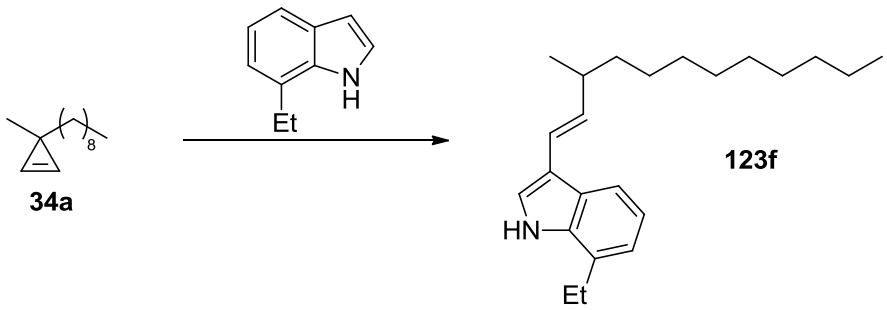
Procedure A: Using **34a** (14.6 mg, 0.081 mmol) to yield 77% of **123d** by ^{1}H NMR analysis. Procedure B: Using **34a** (15.3 mg, 0.085 mmol) to yield **123d** (8.1 mg, 0.024 mmol, 44%). Purified using eluent system of 6:1 hexane:diethyl ether. R_f 0.18 (5:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3426 w (N-H), 2956 m 2923 s 2853 s (C-H), 1657 w (C=C), 1532 w 1420 s (Ar C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, 1H, N<u>H</u>), 7.81 (d, *J* = 2.0 Hz, 1H, H_b), 7.27 (d, *J* = 8.6 Hz, 1H, H_d), 7.20 (d, *J* = 2.5 Hz, 1H, H_a), 7.16 (dd, *J* = 8.6, 2.0 Hz, 1H, H_c), 6.45 (d, *J* = 16.1 Hz, 1H, CH=C<u>H</u>C), 6.02 (dd, *J* = 16.1, 7.9 Hz, 1H, CH=C<u>H</u>CH), 2.28 (m, 1H, C<u>H</u>CH_3), 1.52 – 1.15 (m, 16H, alkyl CH_2), 1.11 (d, *J* = 6.7 Hz, 3H, CHC<u>H</u>$_3$), 0.87 (t, *J* = 6.7 Hz, 3H, CH_2C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.3 (CH), 135.1 (C), 127.0 (C), 125.9 (C), 123.4 (CH), 122.7 (C), 119.8 (CH), 119.7 (CH), 115.7 (C), 112.3 (CH), 38.0 (CH), 37.5 (CH_2), 32.1 (CH_2), 30.0 (CH_2), 29.8 (2 × CH_2), 29.5 (CH_2), 27.7 (CH_2), 22.9 (CH_2), 21.1 (CH_3), 14.3 (CH_3). Found (APCI) $[M+H]^+$ 332.2134, $C_{21}H_{31}ClN$ requires 332.2140.

(*E*)-6-Chloro-3-(3-methyldodec-1-en-1-yl)-1H-indole **123e**:



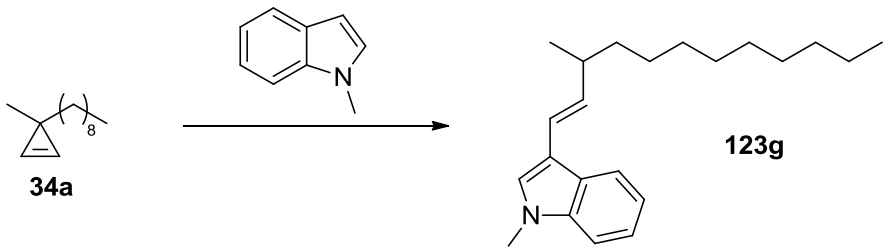
Procedure A: Using **34a** (10.1 mg, 0.056 mmol) to yield 66% of **123e** by ^{1}H NMR analysis. Procedure B: Using **34a** (15.2 mg, 0.084 mmol) to yield **123e** (5.7 mg, 0.017 mmol, 33%). Purified using an eluent system of 10:1 hexane:diethyl ether. Yellow oil obtained. R_f 0.21 (5:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3421 w (N-H), 2960 m 2954 s 2853 m (C-H), 1657 w (C=C), 1532 w 1455 m (Ar C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H, NH), 7.78 (d, *J* = 8.5 Hz, 1H, CClCHCHC), 7.38 (d, *J* = 1.9 Hz, 1H, CCHNH), 7.20 (d, *J* = 1.9 Hz, 1H, CClCHC), 7.16 (dd, *J* = 8.5, 1.9 Hz, 1H, CClCHCH), 6.50 (d, *J* = 16.1 Hz, 1H, CH=CHC), 6.08 (dd, *J* = 16.1, 7.9 Hz, 1H, CH=CHCH), 2.32 (m, 1H, $CHCH_3$), 1.49 – 1.19 (m, 16H, alkyl CH_2), 1.13 (d, *J* = 6.7 Hz, 3H, $CHCH_3$), 0.91 (t, *J* = 6.9 Hz, 3H, CH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.2 (C), 135.3 (CH), 128.3 (C), 124.6 (C), 122.6 (CH), 121.1 (CH), 120.8 (CH), 119.8 (CH), 116.0 (C), 111.3 (CH), 37.9 (CH), 37.6 (CH_2), 32.1 (CH_2), 30.0 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 27.6 (CH_2), 22.9 (CH_2), 21.1 (CH_3), 14.3 (CH_3). Found (EI) $[M]^+$ 331.2056, $C_{21}H_{30}ClN$ requires 331.2061.

(*E*)-7-Ethyl-3-(3-methyldodec-1-en-1-yl)-1H-indole **123f**:



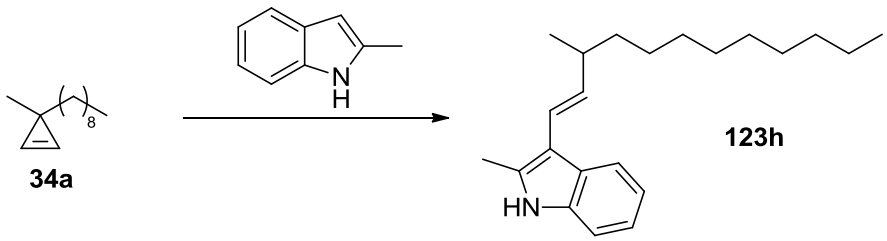
Procedure A: Using **34a** (15.4 mg, 0.085 mmol) to yield 63% of **123f** by ^{1}H NMR analysis. Procedure B: Using **34a** (29.6 mg, 0.164 mmol) to yield **123f** (6.7 mg, 0.021 mmol, 18%). Purified using an eluent system of 10:1 hexane:diethyl ether. Yellow oil obtained. R_f 0.29 (5:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3419 m (N-H), 2958 m 2922 s 2853 s (C-H), 1655 w (C=C), 1533 w 1456 m 1434 m (Ar C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H, N<u>H</u>), 7.72 (d, *J* = 7.5 Hz, 1H, Ar-H), 7.18 (d, *J* = 2.5 Hz, 1H, Ar-H), 7.12 (t, *J* = 7.5 Hz, 1H, C5-<u>H</u>), 7.05 (d, *J* = 7.5 Hz, 1H, Ar-H), 6.51 (d, *J* = 16.0 Hz, 1H, CH=C<u>H</u>C), 6.07 (dd, *J* = 16.0, 7.9 Hz, 1H, CH=C<u>H</u>CH), 2.85 (q, *J* = 7.6 Hz, 2H, CC<u>H$_2$</u>CH$_3$), 2.28 (m, 1H, C<u>H</u>CH$_3$), 1.46 – 1.18 (m, 19H, alkyl CH_2 + CCH_2C<u>H$_3$</u>), 1.10 (d, *J* = 6.7 Hz, 3H, CHC<u>H$_3$</u>), 0.87 (t, *J* = 6.7 Hz, 3H, CH_2CH_2C<u>H$_3$</u>). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7 (C), 134.6 (CH), 126.6 (C), 125.6 (C), 121.8 (CH), 121.0 (CH), 120.4 (CH), 120.4 (CH), 118.0 (CH), 116.3 (C), 38.0 (CH), 37.7 (CH_2), 32.1 (CH_2), 30.0 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 27.7 (CH_2), 24.1 (CH_2), 22.9 (CH_3), 21.2 (CH_2), 14.3 (CH_3), 14.0 (CH_3). Found (CI (NH_3)) $[M+H]^+$ 326.2841, $C_{23}H_{36}N$ requires 326.2842.

(*E*)-N-Methyl-3-(3-methyldodec-1-en-1-yl)-1H-indole **123g**:



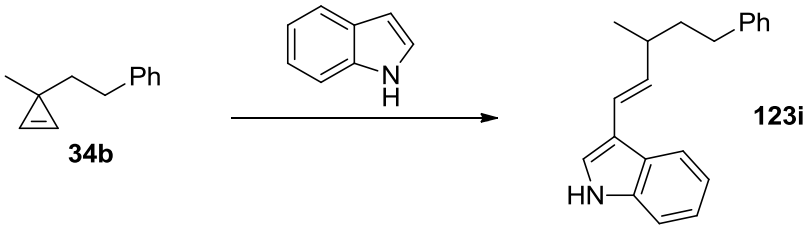
Procedure A: Using **34a** (15.5 mg, 0.086 mmol) to yield 91% of **123g** by ^{1}H NMR analysis. Procedure B: Using **34a** (15.2 mg, 0.084 mmol) to yield **123g** (19.4 mg, 0.062 mmol, 74%). Purified using a gradient eluent system of neat hexane → 20:1 hexane:diethyl ether. Colourless oil obtained. R_f 0.58 (5:1 hexane:diethyl ether); ν_{max}/cm^{-1} 2922 s 2852 m (C-H), 1654 w (C=C), 1466 m (Ar C-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 – 7.81 (m, 1H, Ar-H), 7.31-7.13 (m, 4H, Ar-H), 7.05 (s, 1H, Ar-H), 6.50 (d, *J* = 16.0 Hz, 1H, CH=C<u>H</u>C), 6.03 (dd, *J* = 16.0, 7.9 Hz, 1H, CHC<u>H</u>=CH), 3.76 (s, 3H, NC<u>H</u>$_3$), 2.34 – 2.22 (m, 1H, CH_3C<u>H</u>), 1.46 – 1.18 (m, 16H, alkyl CH_2), 1.10 (d, *J* = 6.7 Hz, 3H, CHC<u>H</u>$_3$), 0.88 (t, *J* = 6.7 Hz, 3H, CH_2C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6 (C), 134.0 (CH), 127.0 (CH), 126.4 (C), 122.0 (CH), 120.3 (CH), 120.2 (CH), 119.6 (CH), 114.2 (C), 109.4 (CH), 38.0 (CH_3), 37.7 (CH_2), 32.8 (CH), 32.1 (CH_2), 30.0 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 27.7 (CH_2), 22.9 (CH_2), 21.3 (CH_3), 14.3 (CH_3). Found (APCI) $[M+H]^+$ 312.2686, $C_{22}H_{34}N$ requires 312.2686.

(*E*)-2-Methyl-3-(3-methyldodec-1-en-1-yl)-1H-indole **123h**:



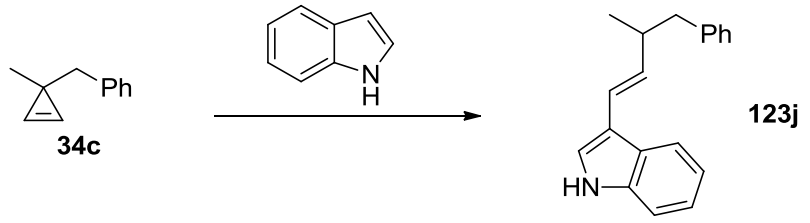
Procedure A: Using **34a** (15.4 mg, 0.085 mmol) to yield 64% of **123h** by ^{1}H NMR analysis. Procedure B: Using **34a** (15.2 mg, 0.084 mmol) to yield **123h** (9.2 mg, 0.030 mmol, 52%). Purified using an eluent system of 7:1 hexane:diethyl ether. R_f 0.25 (5:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3401 m (N-H), 2955 m 2922 s 2853 s (C-H), 1651 (C=C), 1552 w 1488 w 1460 (Ar C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (m, 2H, Ar-H, NH), 7.32 – 7.21 (m, 1H, Ar-H), 7.18 – 7.07 (m, 2H, Ar-H), 6.47 (d, *J* = 16.0 Hz, 1H, CH=C<u>H</u>C), 6.00 (dd, *J* = 16.0, 8.0 Hz, 1H, CHC<u>H</u>=CH), 2.45 (s, 3H, CC<u>H</u>$_3$), 2.30 (m, 1H, C<u>H</u>CH_3), 1.46 – 1.19 (m, 16H, alkyl CH_2), 1.12 (d, *J* = 6.7 Hz, 3H, CHC<u>H</u>$_3$), 0.88 (t, *J* = 6.7 Hz, 3H, CH_2C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6 (C), 134.8 (CH), 132.4 (C), 127.1 (C), 121.5 (CH), 120.1 (CH), 120.0 (CH), 119.6 (CH), 111.1 (C), 110.4 (CH), 38.4 (CH), 37.8 (CH_2), 32.1 (CH_2), 30.0 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 27.7 (CH_2), 22.9 (CH_2), 21.5 (CH_3), 14.3 (CH_3), 12.4 (CH_3). Found (APCI) $[M+H]^+$ 312.2680, $C_{22}H_{34}N$ requires 312.2686.

(*E*)-3-(3-Methyl-5-phenylpent-1-en-1-yl)-1H-indole **123i**:



Procedure A: Using **34b** (15.2 mg, 0.096 mmol) to yield 81% of **123i** by ^{1}H NMR analysis. Procedure B: Using **34b** (19.8 mg, 0.110 mmol) to yield **123i** (29.3 mg, 0.185 mmol, 15%). Purified using an eluent system of 8:1 hexane:diethyl ether. Yellow oil obtained. R_f 0.26 (5:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3412 m (N-H), 3026 m 2923 m 2855 m (C-H), 1655 w (C=C), 1532 w 1495 m 1455 s (Ar C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (s, 1H, NH), 7.88 (d, *J* = 7.2 Hz, 1H, Ar-H), 7.46 – 7.07 (m, 9H, Ar-H), 6.56 (d, *J* = 16.0 Hz, 1H, CH=CHC), 6.11 (dd, *J* = 16.0, 8.0 Hz, 1H, CHCH=CH), 2.80 – 2.58 (m, 2H, CH_2Ph), 2.36 (m, 1H, $CHCH_3$), 1.79-1.71 (m, , 2H, CH_2CH_2Ph), 1.17 (d, *J* = 6.7 Hz, 3H, $CHCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1 (C), 136.9 (C), 133.9 (CH), 128.6 (CH), 128.4 (CH), 125.9 (C), 125.7 (CH), 122.5 (CH), 122.4 (CH), 121.1 (CH), 120.2 (CH), 120.2 (CH), 115.7 (C), 111.4 (CH), 39.3 (CH_2), 37.7 (CH), 34.0 (CH_2), 21.3 (CH_3). Found (ESI) $[M+OH]^+$ 292.1699, $C_{20}H_{22}NO$ requires 292.1696.

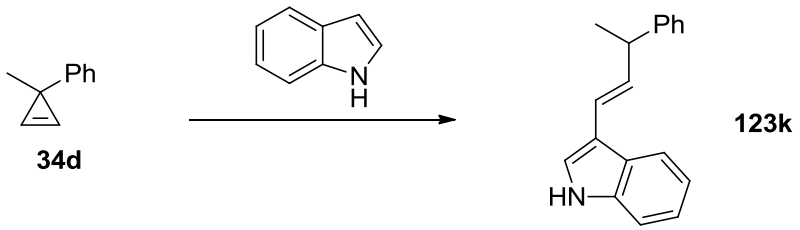
(*E*)-3-(3-Methyl-4-phenylbut-1-en-1-yl)-1H-indole **123j**:



Procedure A: Using **34c** (15.4 mg, 0.107 mmol) to yield 73% of **123j** by ^{1}H NMR analysis. Procedure B: Using **34c** (30.6 mg, 0.212 mmol) to yield **123j** (5.2 mg, 0.020 mmol, 14%). Purified using an eluent system of 10:1 hexane:diethyl ether. Yellow oil obtained. R_f 0.18 (5:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3413 m (N-H), 2956 m 2922 m 2867 m (C-H), 1655 w (C=C), 1532 w 1495 m 1455 m (Ar C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H, NH), 7.82 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.42 – 7.09 (m, 9H, Ar-H), 6.50 (d, *J* = 16.1 Hz, 1H, CH=CHC), 6.18 (dd, *J* = 16.1, 6.9 Hz, 1H, CHCH=CH), 2.83

(m, 1H, C<u>H</u>CH$_3$), 2.87 – 2.78 (m, 2H, CHC<u>H$_2$</u>C), 1.12 (d, *J* = 6.4 Hz, 3H, CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$) δ 141.1 (C), 136.9 (C), 133.4 (CH), 129.5 (CH), 128.3 (CH), 125.9 (CH), 125.8 (C), 122.5 (CH), 122.4 (CH), 120.7 (CH), 120.2 (2 × CH), 115.7 (C), 111.4 (CH), 44.2 (CH), 39.5 (CH$_2$), 20.2 (CH$_3$). Found (EI) $[M]^+$ 261.1510, $C_{19}H_{19}N$ requires 261.1512.

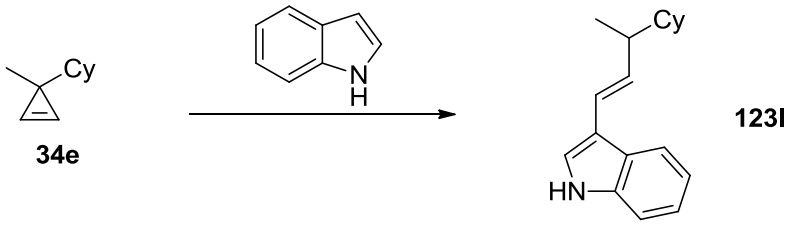
(*E*)-3-(3-Phenylbut-1-en-1-yl)-1H-indole **123k:**



34d **123k**

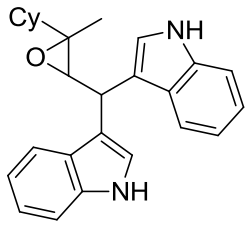
Procedure A: Using **34d** (15.5 mg, 0.119 mmol) to yield 83% of **123k** by ^{1}H NMR analysis. Procedure B: Using **34d** (20.9 mg, 0.161 mmol) to yield **123k** (9.2 mg, 0.037 mmol, 35%). Purified using a gradient eluent system of neat hexane → 2:1 hexane:diethyl ether. Yellow oil obtained. R_f 0.19 (5:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3412 s (N-H), 2962 m 2926 w 2869 w (C-H), 1652 m (C=C), 1530 w 1491 m 1455 m (Ar C=C); ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.03 (s, 1H, N<u>H</u>), 7.86 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.37 – 7.33 (m, 5H, Ar-H), 7.25 – 7.11 (m, 4H, Ar-H), 6.61 (dd, *J* = 16.1, 0.8 Hz, 1H, CHCH=C<u>H</u>), 6.40 (dd, *J* = 16.1, 6.7 Hz, 1H, CHC<u>H</u>=CH), 3.68 (m, 1H, CH$_3$C<u>H</u>), 1.51 (d, *J* = 7.0 Hz, 3H, CHC<u>H$_3$</u>); ^{13}C NMR (75 MHz, CDCl$_3$) δ 146.5 (C), 136.9 (C), 132.6 (CH), 128.6 (CH), 127.5 (CH), 126.2 (CH), 125.8 (C), 122.7 (CH), 122.5 (CH), 121.2 (CH), 120.2 (2 × CH), 115.5 (C), 111.4 (CH), 43.2 (CH), 21.8 (CH$_3$). Found (EI) $[M]^+$ 247.1354, $C_{18}H_{17}N$ requires 247.1356.

(*E*)-3-(3-Cyclohexylbut-1-en-1-yl)-1H-indole **123l:**



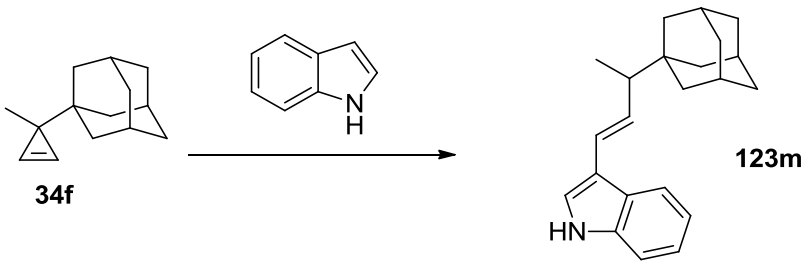
Procedure A: Using **34e** (15.2 mg, 0.112 mmol) to yield 70% of **123l** by ^{1}H NMR analysis. Procedure B: Using **34e** (19.6 mg, 0.144 mmol) to yield **123l** (10.2 mg, 0.040 mmol, 40%). Purified using a gradient eluent system of neat hexane → 10:1 hexane:diethyl ether. Yellow oil obtained. R_f 0.21 (5:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3409 m (N-H), 2921 m 2849 m (C-H), 1653 w (C=C), 1532 w 1456 m (Ar C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (s, 1H, NH), 7.87 (dd, *J* = 8.1, 1.0 Hz, 1H, Ar-H), 7.39 – 7.32 (m, 1H, Ar-H), 7.25 – 7.12 (m, 3H, Ar-H), 6.49 (d, *J* = 16.0 Hz, 1H, CHCH=CH), 6.11 (dd, *J* = 16.0, 8.4 Hz, 1H, CHCH=CH), 2.22 – 2.05 (m, 1H, CH_3CH), 1.90 – 1.57 (m, 5H, cyclohexyl H), 1.36 – 0.91 (m, 6H, cyclohexyl H), 1.10 (d, *J* = 6.8 Hz, 3H, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.9 (C), 133.2 (CH), 125.9 (C), 122.5 (CH), 122.2 (CH), 121.0 (CH), 120.3 (CH), 120.1 (CH), 115.9 (C), 111.3 (CH), 43.8 (CH), 43.7 (CH), 30.8 (CH_2), 30.6 (CH_2), 26.9 (CH_2), 18.2 (CH_3). Found (APCI) $[M+H]^+$ 254.1904, $C_{18}H_{24}N$ requires 254.1903.

Note: Traces of **127e** were also detected (7%) in the crude ^{1}H NMR; identification was by comparison to pure samples of **127a** and **127f**, as isolation for characterisation of **127e** was unsuccessful. In addition, subjection of **34e** to O_2 conditions (see Table 2.9) still produces **123l** as the major product, with **127e** produced only in traces.



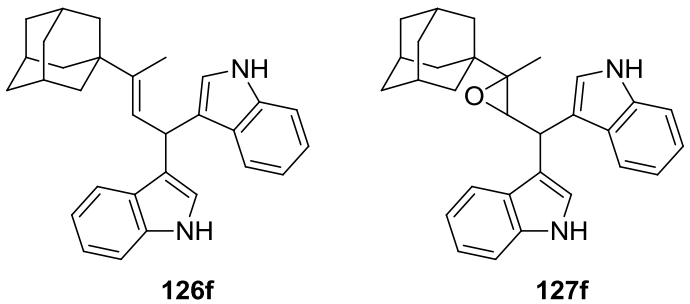
127e

(*E*)-3-(3-(Adamantan-1-yl)but-1-en-1-yl)-1H-indole **123m:**

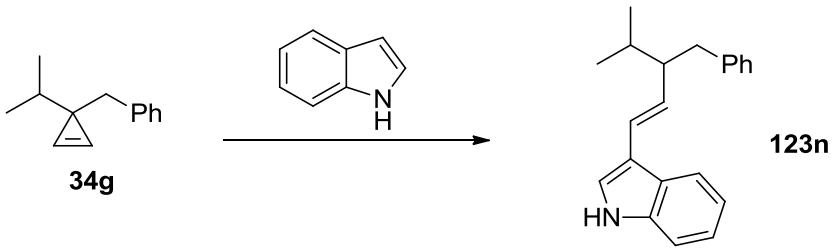


Procedure A: Using **34f** (14.6 mg, 0.078 mmol) to yield 81% of **123m** by ^{1}H NMR analysis. Procedure B: Using **34f** (15.0 mg, 0.080 mmol) to yield **123m** (8.5 mg, 0.029 mmol, 50%). Purified using an eluent system of 20:1 hexane:diethyl ether. White film obtained. R_f 0.22 (5:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3413 m (N-H), 2900 s 2847 m (C-H), 1652 w (C=C), 1532 w 1456 m (Ar C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H, N<u>H</u>), 7.91 – 7.83 (m, 1H, Ar-H), 7.40 – 7.33 (m, 1H, Ar-H), 7.25 – 7.13 (m, 3H, Ar-H), 6.48 (d, *J* = 16.0 Hz, 1H, CHCH=C<u>H</u>), 6.16 (dd, *J* = 16.0, 9.1 Hz, 1H, CHC<u>H</u>=CH), 2.08 – 1.46 (m, 16H, Alkyl H), 1.04 (d, *J* = 7.0 Hz, 3H, CHC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.9 (C), 131.1 (CH), 125.8 (C), 122.5 (CH), 122.3 (CH), 121.9 (CH), 120.3 (CH), 120.2 (CH), 116.0 (C), 111.4 (CH), 49.2 (CH), 40.2 (CH_2), 37.6 (CH_2), 35.2 (C), 29.0 (CH), 14.4 (CH_3). Found (EI) $[M]^+$ 305.2139, $C_{22}H_{27}N$ requires 305.2138.

Note: **126f** and **127f** were detected as trace products in 5% and 8% yield respectively by analysis of the crude NMR. See pages 110 and 111 for characterisation of **126f** and **127f** respectively.



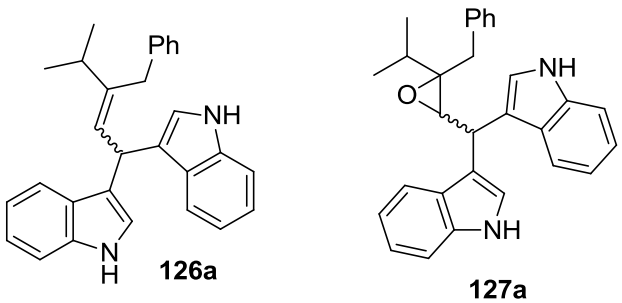
(*E*)-3-(3-Benzyl-4-methylpent-1-en-1-yl)-1H-indole **123n:**



34g **123n**

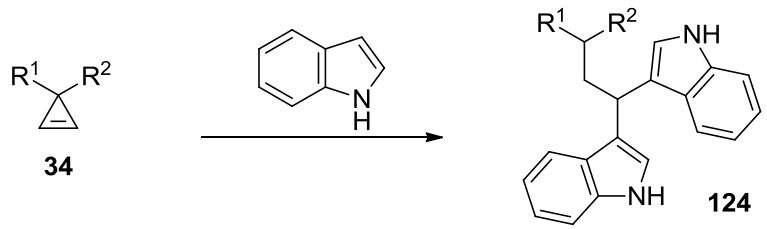
Procedure A: Using **34g** (15.0 mg, 0.087 mmol) to yield 28% of **123n** by ^{1}H NMR analysis. Procedure B: Using **34g** (20.6 mg, 0.120 mmol) to yield **123n** (3.3 mg, 0.011 mmol, 14%). Purified using a gradient eluent system of neat hexane → 9:1 hexane:diethyl ether. Yellow oil obtained. R_f 0.15 (5:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3415 m (N-H), 2957 m 2926 w 2869 w (C-H), 1653 w (C=C), 1522 w 1494 w 1456 m (Ar C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H, NH), 7.81 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.44 – 7.03 (m, 9H, Ar-H), 6.34 (d, *J* = 16.0 Hz, 1H, CHCH=CH), 6.04 (dd, *J* = 16.0, 9.1 Hz, 1H, CHCH=CH), 2.86 (dd, *J* = 13.5, 6.1 Hz, 1H, CHHPh), 2.72 (dd, *J* = 13.5, 8.2 Hz, 1H, CHHPh), 2.38 – 2.24 (m, 1H, CH_3CHCH_3), 1.86 – 1.69 (m, 1H, $CHCHCH_2$), 1.00 (d, *J* = 6.8 Hz, 3H, $CHCH_3$), 0.98 (d, *J* = 6.8 Hz, 3H, $CHCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.6 (C), 136.8 (C), 129.5 (CH), 129.1 (C), 128.2 (CH), 125.7 (CH), 123.6 (CH), 122.4 (CH), 120.3 (CH), 120.2 (CH), 115.9 (C), 111.4 (CH), 52.2 (CH), 39.7 (CH_2), 31.3 (CH), 21.4 (CH_3), 18.5 (CH_3). Found (APCI) $[M+H]^+$ 290.1902, $C_{21}H_{24}N$ requires 290.1903.

Note: **126a** and **127a** were detected as trace products in 15% and 28% yield respectively by analysis of the crude NMR. See pages 112 and 113 for characterisation of **126a** and **127a** respectively.



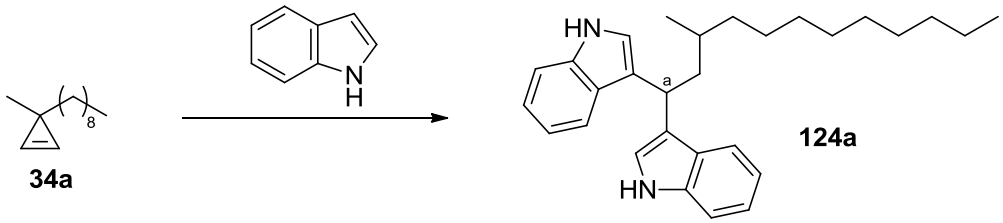
126a **127a**

***Bis*-indolylalkane 124 general synthetic procedure:**



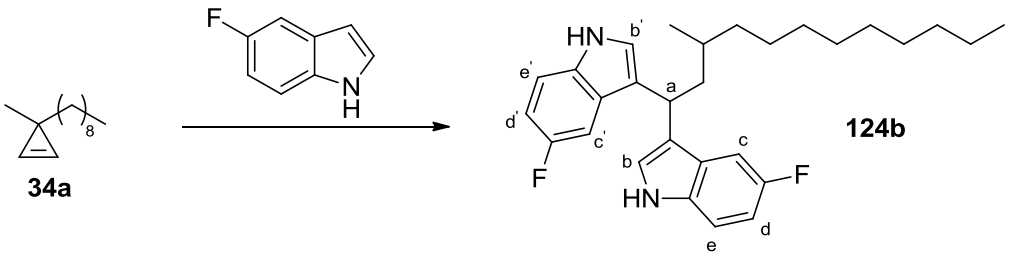
To a solution of cyclopropene (1 equiv.) and indole (2.2 equiv.) in DCM (0.14 M), 5 mol% of catalyst **1** was added. The solution was allowed to stir for 48 h at reflux. The reaction was allowed to cool to room temperature, concentrated under reduced pressure and purified by flash column chromatography.

3,3'-(3-Methyldodecane-1,1-diyl)*bis*(1H-indole) **124a**:



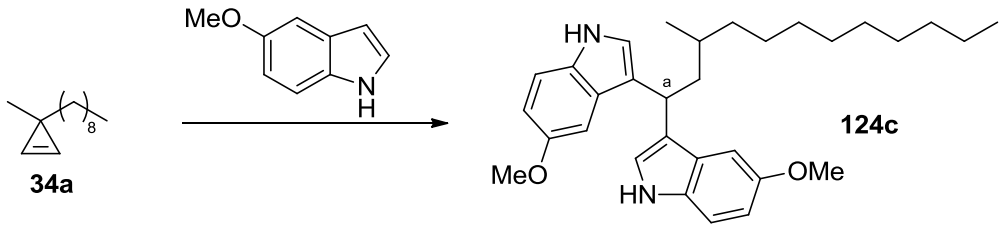
Purified using a gradient eluent system of 5:1 → 2:1 hexane:diethyl ether. Pale yellow oil obtained. R_f 0.18 (2:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3413 s (N-H), 2954 m 2924 s 2853 s (C-H) 1456 s (Ar C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, H, NH), 7.84 (s, H, NH), 7.72 – 7.57 (m, 2H, Ar-H), 7.33 (dd, *J* = 8.0, 5.5 Hz, 2H, Ar-H), 7.17 (t, *J* = 7.3 Hz, 2H, Ar-H), 7.06 (m, 3H, Ar-H), 6.91 (s, 1H, Ar-H), 4.70 – 4.59 (m, 1H, H_a), 2.33 – 1.94 (m, 2H, CHCH_2CH), 1.67 – 1.10 (m, 17H, long chain alkyl H), 1.00 (d, *J* = 6.6 Hz, 3H, CHCH_3), 0.90 (t, *J* = 6.8 Hz, 3H, CH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.8 (2 × C), 127.4 (C), 127.2 (C), 121.9 (2 × CH), 121.6 (CH), 121.5 (CH), 121.3 (C), 120.3 (C), 119.9 (CH), 119.7 (CH), 119.2 (2xCH), 111.2 (2 × CH), 43.5 (CH_2), 37.5 (CH_2), 32.1 (CH_2), 31.6 (CH), 30.8 (CH), 30.2 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 27.1 (CH_2), 22.9 (CH_2), 20.1 (CH_3), 14.3 (CH_3); Found (APCI) $[M]^+$ 414.3018, $C_{29}H_{38}N_2$ requires 414.3030.

3,3'-(3-Methyldodecane-1,1-diyl)*bis*(5-fluoro-1H-indole) **124b**:



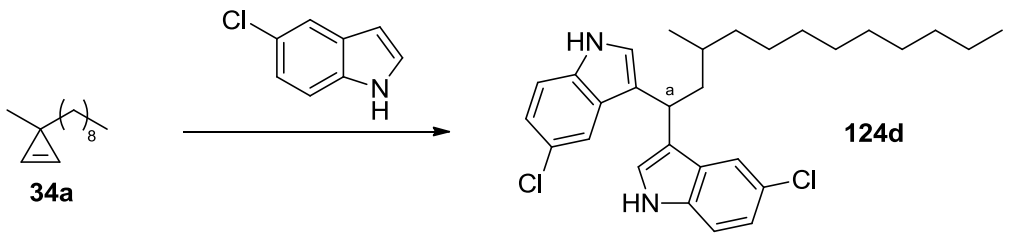
Purified using an eluent system of 2:1 hexane:diethyl ether. Pale yellow oil obtained. R_f 0.15 (2:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3473 m 3429 m (N-H), 2954 m 2923 s 2853 s (C-H), 1627 m 1580 m (Ar C=C) 1167 s (C-F); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 1H, N<u>H</u>), 7.89 (s, 1H, N<u>H</u>), 7.19 – 7.05 (m, 4H, $H_{c/c'}/H_{e/e'}$), 7.02 (d, *J* = 2.4 Hz, 1H, $H_b/H_{b'}$), 6.93 (d, *J* = 2.3 Hz, 1H, $H_b/H_{b'}$), 6.80 (app. td, *J* = 9.1, 2.6 Hz, 2H, $H_{d/d'}$), 4.37 (dd, *J* = 8.9, 6.5 Hz, 1H, H_a), 2.19 – 1.78 (m, 2H, CHC<u>H_2</u>CH), 1.55 – 0.97 (m, 17H, long alkyl chain H), 0.89 (d, *J* = 6.5 Hz, 3H, CHC<u>H_3</u>), 0.80 (t, *J* = 6.8 Hz, 3H, CH_2C<u>H_3</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4 (d, *J* = 233.8 Hz, 2 × C-F), 133.15 (2 × C), 127.4 (d, *J* = 9.4 Hz, C), 127.2 (d, *J* = 9.4 Hz, C), 123.2 (CH), 123.1 (CH), 120.7 (d, *J* = 4.8 Hz, C), 119.7 (d, *J* = 4.8 Hz, C), 111.7 (d, *J* = 9.7 Hz, 2 × CH), 110.4 (CH), 110.0 (CH), 104.6 (d, *J* = 23.5 Hz, CH), 104.4 (d, *J* = 23.5 Hz, CH), 42.7 (CH_2), 37.4 (CH_2), 32.1 (CH_2), 31.8 (CH), 30.7 (CH), 30.1 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 27.0 (CH_2), 22.8 (CH_2), 20.0 (CH_3), 14.3 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ -124.9 (td, *J* = 9.6, 4.4 Hz); Found (APCI) $[M]^+$ 450.2829, $C_{29}H_{36}F_2N_2$ requires 450.2841.

3,3'-(3-Methyldodecane-1,1-diyl)*bis*(5-methoxy-1H-indole) **124c:**



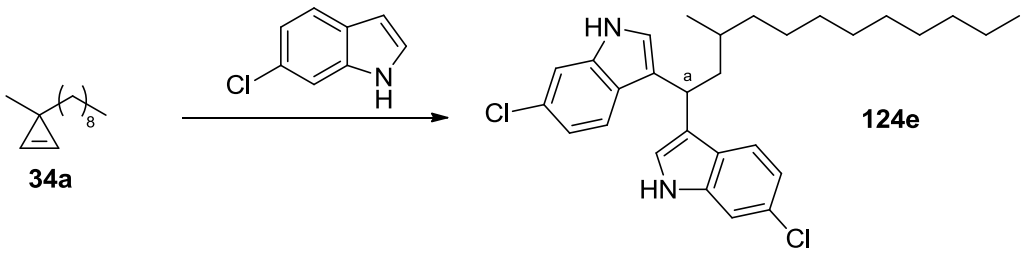
Purified using a gradient eluent system of 10:1 → 2:1 hexane:diethyl ether. Colourless oil obtained. R_f 0.12 (2:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3413 s (N-H), 2922 s 2852 s (C-H), 1624 s 1581 s 1482 s 1454 s 1438 s (Ar C=C), 1208 s (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (s, H, NH), 7.75 (s, H, NH), 7.22 (d, *J* = 8.8 Hz, H, Ar-H), 7.21 (d, *J* = 8.8 Hz, H, Ar-H), 7.10 (d, *J* = 2.4 Hz, H, Ar-H), 7.08 (d, *J* = 2.4 Hz, H, Ar-H), 7.00 (d, *J* = 2.4 Hz, 1H, Ar-H), 6.90 (d, *J* = 2.4 Hz, 1H, Ar-H), 6.83 (dd, *J* = 8.8, 2.4 Hz, 2H, Ar-H), 4.52 (dd, *J* = 8.8, 6.4 Hz, 1H, H_a), 3.81 (s, 3H, OCH$_3$), 3.79 (s, 3H, OCH$_3$), 2.31 – 1.92 (m, 2H, CHCH$_2$CH), 1.62 – 1.13 (m, 17H, long alkyl chain H), 1.01 (d, *J* = 6.5 Hz, 3H, CHCH$_3$), 0.90 (t, *J* = 6.8 Hz, 3H, CH$_2$CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7 (2 × C), 132.0 (C), 131.9 (C), 127.8 (C), 127.6 (C), 122.4 (CH), 122.4 (CH), 120.9 (C), 119.8 (C), 111.8 (CH), 111.8 (CH), 111.6 (2 × CH), 102.0 (CH), 102.0 (CH), 56.0 (2 × CH_3), 43.1 (CH_2), 37.6 (CH_2), 32.1 (CH_2), 31.6 (CH), 30.8 (CH), 30.2 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 27.1 (CH_2), 22.8 (CH_2), 20.2 (CH_3), 14.3 (CH_3); Found (APCI) $[M]^+$ 474.3236, $C_{31}H_{42}N_2O_2$ requires 474.3241.

3,3'-(3-Methyldodecane-1,1-diyl)*bis*(5-chloro-1H-indole) **124d:**



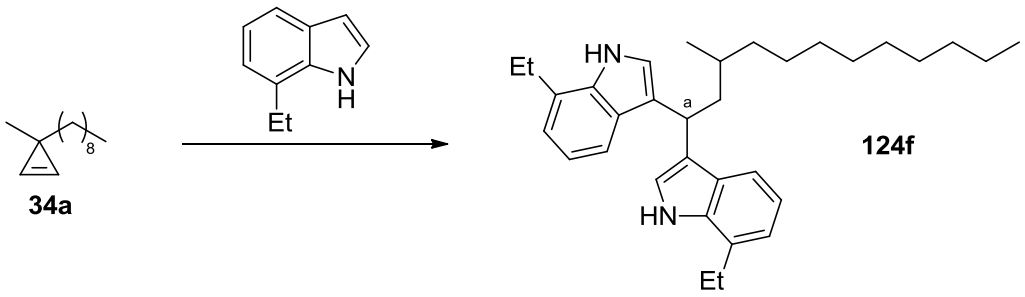
Purified using a gradient eluent system of 3:1 → 2:1 hexane:diethyl ether. Colourless oil obtained. R_f 0.11 (2:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3430 m (N-H), 2923 s 2853 s (C-H), 1461 s (Ar C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 1H, N<u>H</u>), 7.91 (s, 1H, N<u>H</u>), 7.53-7.50 (m, 2H, Ar-H), 7.26-7.22 (m, 2H, Ar-H), 7.17 – 7.04 (m, 3H, Ar-H), 6.99 (d, *J* = 2.3 Hz, 1H, Ar-H), 4.48 (dd, *J* = 8.9, 6.6 Hz, 1H, H_a), 2.20 (ddd, *J* = 14.0, 8.9, 5.3 Hz, 1H, CH_aC<u>H</u>HCH), 2.01 – 1.87 (m, 1H, CH_aCH<u>H</u>CH), 1.54 – 1.09 (m, 17H, alkyl H), 0.97 (d, *J* = 6.5 Hz, 3H, CHC<u>H</u>$_3$), 0.89 (t, *J* = 6.8 Hz, 3H, CH_2C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.1 (2 × C), 128.2 (C), 128.1 (C), 124.9 (2 × C), 123.0 (CH), 122.8 (CH), 122.3 (2 × CH), 120.5 (C), 119.5 (C), 119.2 (CH), 119.1 (CH), 112.3 (2 × CH), 42.8 (CH_2), 37.3 (CH_2), 32.1 (CH_2), 31.7 (CH), 30.7 (CH), 30.1 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 27.1 (CH_2), 22.8 (CH_2), 20.0 (CH_3), 14.3 (CH_3). Found (ESI) $[M+NH_4]^+$ 500.2589, $C_{29}H_{40}Cl_2N_3$ requires 500.2594.

3,3'-(3-Methyldodecane-1,1-diyl)*bis*(6-chloro-1H-indole) **124e:**



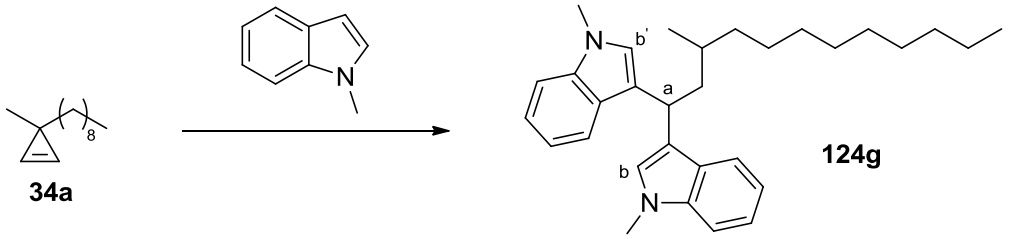
Purified using a gradient eluent system of 4:1 → 2:1 hexane:diethyl ether. Yellow oil obtained. R_f 0.20 (2:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3427 m (N-H), 2924 s 2854 m (C-H), 1531 m 1455 m (Ar C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1H, NH), 7.87 (s, 1H, NH), 7.45 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.44 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.32 (d, *J* = 1.5 Hz, 1H, Ar-H), 7.32 (d, *J* = 1.5 Hz, 1H, Ar-H), 7.07 – 6.96 (m, 3H, Ar-H), 6.93 (d, *J* = 2.3 Hz, 1H, Ar-H), 4.52 (dd, *J* = 8.9, 6.5 Hz, 1H, H_a), 2.25 – 1.85 (m, 2H, CHCH_2CH), 1.51 – 1.07 (m, 17H, alkyl H), 0.97 (d, *J* = 6.5 Hz, 3H, CHCH_3), 0.88 (t, *J* = 6.8 Hz, 3H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.0 (2 × C), 127.9 (2 × C), 125.8 (C), 125.7 (C), 122.1 (CH), 122.0 (CH), 121.1 (C), 120.6 (CH), 120.4 (CH), 120.1 (C), 120.0 (2 × CH), 111.2 (2 × CH), 43.1 (CH_2), 37.4 (CH_2), 32.1 (CH_2), 31.5 (CH), 30.7 (CH), 30.1 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 27.0 (CH_2), 22.8 (CH_2), 20.1 (CH_3), 14.3 (CH_3). Found (EI) $[M]^+$ 482.2245, $C_{29}H_{36}Cl_2N_2$ requires 482.2250.

3,3'-(3-Methyldodecane-1,1-diyl)*bis*(7-ethyl-1H-indole) **124f:**



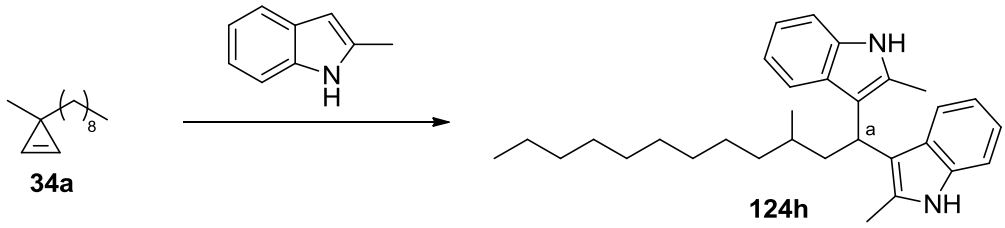
Purified using a gradient eluent system of 4:1 → 2:1 hexane:diethyl ether. Yellow oil obtained. R_f 0.25 (2:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3423 m (N-H), 2961 m 2924 s 2853 m (C-H), 1462 m 1434 m (Ar C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (s, 1H, N<u>H</u>), 7.77 (s, 1H, N<u>H</u>), 7.54-7.47 (m, 2H, Ar-H), 7.08 – 6.95 (m, 5H, Ar-H), 6.90 (d, *J* = 2.2 Hz, 1H, Ar-H), 4.62 (dd, *J* = 8.9, 6.4 Hz, 1H, H_a), 2.88-2.79 (m, 4H, 2 × C<u>H</u>$_2$CH$_3$), 2.33 – 1.92 (m, 2H, CHC<u>H</u>$_2$CH), 1.63 – 1.11 (m, 17H, alkyl H), 0.99 (d, *J* = 6.5 Hz, 3H, CHC<u>H</u>$_3$), 0.89 (t, *J* = 6.8 Hz, 3H, CH$_2$C<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.6 (2 × C), 127.2 (C), 126.9 (C), 126.5 (C), 126.4 (C), 121.9 (C), 121.2 (CH), 121.1 (CH), 120.8 (C), 120.3 (CH), 120.3 (CH), 119.4 (CH), 119.4 (CH), 117.7 (CH), 117.5 (CH), 43.6 (CH_2), 37.5 (CH_2), 32.1 (CH_2), 31.7 (CH), 30.9 (CH), 30.2 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 27.0 (CH_2), 24.1 (CH_2), 22.9 (CH_2), 20.1 (CH_2), 14.3 (CH_3), 13.9 (CH_3), 13.9 (2 × CH_3). Found (ESI) $[M+NH_4]^+$ 488.3994, $C_{33}H_{50}N_3$ requires 488.3999.

3,3'-(3-Methyldodecane-1,1-diyl)*bis*(1-methyl-1H-indole) **124g:**



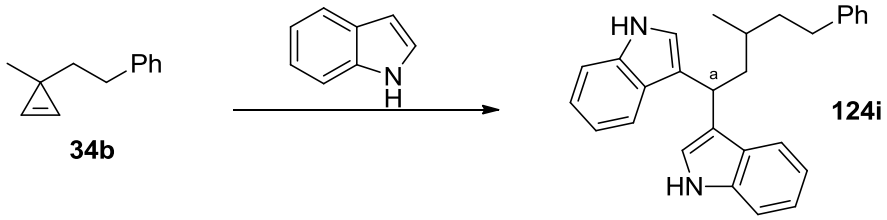
Purified using a gradient eluent system of 10:1 → 4:1 hexane:diethyl ether. Yellow oil obtained. R_f 0.52 (2:1 hexane:diethyl ether); ν_{max}/cm^{-1} 2953 s 2923 s 2853 s (C-H) 1615 w 1548 w 1467 m (Ar C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 – 7.50 (m, 2H, Ar-H), 7.21 – 7.15 (m, 2H, Ar-H), 7.15 – 7.05 (m, 2H, Ar-H), 6.96 (m, 2H, Ar-H), 6.89 (s, 1H, H_b), 6.79 (s, 1H, $H_{b'}$), 4.53 (dd, *J* = 8.9, 6.5 Hz, 1H, H_a), 3.64 (s, 3H, NC$\underline{H}_3$), 3.60 (s, 3H, NC$\underline{H}_3$), 2.23 (ddd, *J* = 14.2, 8.9, 5.4 Hz, 1H, CHC$\underline{H}$HCH), 2.06 – 1.92 (m, 1H, CHCH$\underline{H}$CH), 1.56 – 1.01 (m, 17H, long alkyl chain), 0.90 (d, *J* = 6.5 Hz, 3H, CHC$\underline{H}_3$), 0.80 (t, *J* = 6.8 Hz, 3H, $CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.4 (2 × C), 127.8 (C), 127.5(C), 126.4 (CH), 126.3 (CH), 121.4 (2 × CH), 120.0 (C), 119.9(CH), 119.7 (CH), 118.9 (C), 118.5 (2 × CH), 109.2 (CH), 109.2 (CH), 44.0 (CH_2), 37.5 (CH_2), 32.8 (CH_3), 32.7 (CH_3), 32.1 (CH_2), 31.4 (CH), 30.8 (CH), 30.2 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 27.0 (CH_2), 22.9 (CH_2), 20.1 (CH_3), 14.3 (CH_3). Found (APCI) $[M+H]^+$ 443.3418, $C_{31}H_{42}N_2$ requires 443.3421.

3,3'-(3-Methyldodecane-1,1-diyl)*bis*(2-methyl-1H-indole) **124h:**



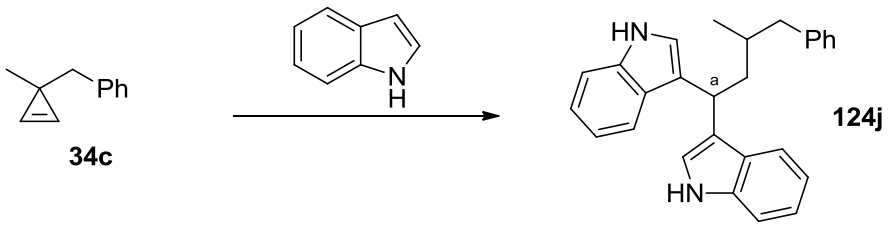
Purified using a gradient eluent system of 5:1 → 2:1 hexane:diethyl ether. White film obtained. R_f 0.28 (2:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3399 m (N-H), 2954 m 2922 s 2853 s (C-H), 1618 w 1584 w 1459 s (Ar C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.52 (s, 1H, NH), 7.50 (s, 1H, NH), 7.08 (d, *J* = 7.9 Hz, 2H, Ar-H), 7.01 – 6.84 (m, 4H, Ar-H), 4.49 (dd, *J* = 9.2, 6.9 Hz, 1H, H_a), 2.39 (ddd, *J* = 14.5, 9.2, 5.3 Hz, 1H, CHCH<u>H</u>CH), 2.19 (s, 3H, CCH_3), 2.16 (s, 3H, CCH_3), 2.19-2.05 (m, 1H, CHC<u>H</u>HCH), 1.50 – 0.99 (m, 17H, long alkyl chain), 0.86 (d, *J* = 6.5 Hz, 3H, CHC<u>H</u>$_3$), 0.80 (t, *J* = 6.8 Hz, 3H, CH_2C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.2 (C), 135.2 (C), 130.9 (C), 130.7 (C), 128.8 (C), 128.7 (C), 120.5 (2 × CH), 119.6 (CH), 119.5 (CH), 119.1 (2 × CH), 115.5 (C), 114.8 (C), 110.2 (2 × CH), 42.2 (CH_2), 37.5 (CH_2), 32.1 (CH), 31.8 (CH), 30.7 (CH_2), 30.2 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 27.0 (CH_2), 22.9 (CH_2), 19.9 (2 × CH_3), 14.3 (CH_3), 12.9 (CH_3). HRMS not successful with repeated attempts, molecule constantly fragmented to 3-(*E*)-vinylindole **123h** in mass spectrometer. All other forms of analysis shows that expected product has formed by presence of characteristic peak of H_a at δ 4.49 ppm in ^{1}H NMR spectrum.

3,3'-(3-Methyl-5-phenylpentane-1,1-diyl)bis(1H-indole) **124i:**



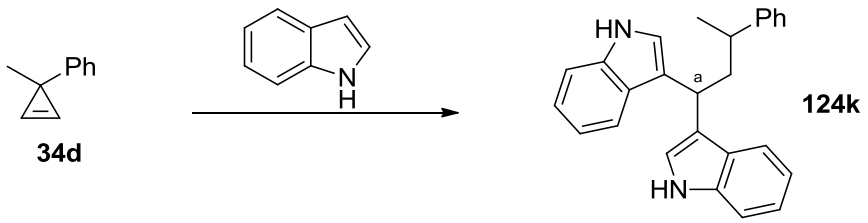
Purified using a gradient eluent system of 4:1 → 2:1 hexane:diethyl ether. Yellow oil obtained. R_f 0.25 (2:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3415 s (N-H), 2924 m 2854 w (C-H), 1495 w 1455 s (Ar C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H, NH), 7.81 (s, 1H, NH), 7.67-7.61 (m, 2H, Ar-H), 7.38 – 7.30 (m, 2H, Ar-H), 7.27 – 7.02 (m, 9H, Ar-H), 6.99 (d, *J* = 2.1 Hz, 1H, Ar-H), 6.88 (dd, *J* = 2.4, 0.6 Hz, 1H, Ar-H), 4.65 (dd, *J* = 9.0, 6.4 Hz, 1H, H_a), 2.62 (ddd, *J* = 13.5, 10.5, 5.5 Hz, 1H, CHHPh), 2.53 (ddd, *J* = 13.5, 10.1, 5.8 Hz, 1H, CHHPh), 2.32 (ddd, *J* = 14.2, 9.0, 5.3 Hz, 1H, CHCHHCH), 2.12 – 2.03 (m, 1H, CHCHHCH), 1.83 – 1.48 (m, 3H, CH_2 + CH), 1.08 (d, *J* = 6.4 Hz, 3H, $CHCH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.3 (C), 136.7 (2 × C), 128.5 (CH), 128.4 (CH), 127.3 (C), 127.1 (C), 125.6 (CH), 121.9 (2 × CH), 121.61 (CH), 121.56 (CH), 121.0 (C), 120.0 (C), 119.9 (CH), 119.6 (CH), 119.2 (2 × CH), 111.23 (CH), 111.20 (CH), 43.2 (CH_2), 39.4 (CH_2), 33.5 (CH_2), 31.7 (CH), 30.7 (CH), 20.1 (CH_3). Found (EI) $[M]^+$ 392.2250, $C_{28}H_{28}N$ requires 392.2247.

3,3'-(3-Methyl-4-phenylbutane-1,1-diyl)bis(1H-indole) **124j:**



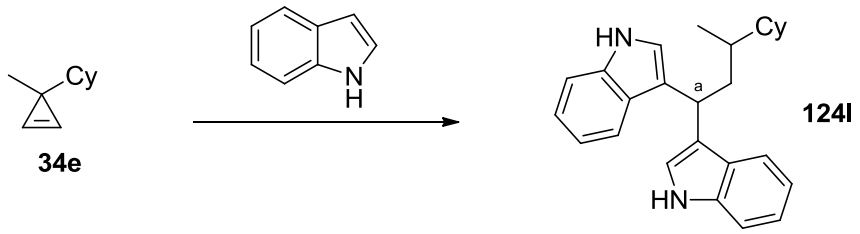
Purified using an eluent system of 4:1 hexane:diethyl ether. Pale yellow oil obtained. R_f 0.15 (2:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3413 s (N-H), 2953 w 2921 m 2820 w (C-H), 1494 w 1455 s (Ar C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (s, 1H, NH), 7.71 (s, 1H, NH), 7.59 (d, *J* = 7.9 Hz, 1H, Ar-H), 7.41 (d, *J* = 7.7 Hz, 1H, Ar-H), 7.24 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.19 – 6.83 (m, 4H, Ar-H), 6.71-6.65 (m, 2H, Ar-H), 4.58 (dd, *J* = 9.5, 5.9 Hz, 1H, H_a), 2.60 (dd, *J* = 13.3, 7.0 Hz, 1H, CHHPh), 2.42 (dd, *J* = 13.3, 7.3 Hz, 1H, CHHPh), 2.19 (ddd, *J* = 14.0, 9.5, 4.8 Hz, 1H, CH_aCHH), 2.03 – 1.88 (m, 1H, CH_aCHH), 1.84-1.73 (m, 1H, CH_3CH), 0.95 (d, *J* = 6.5 Hz, 3H, $CHCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.6 (C), 136.8 (C), 136.7 (C), 129.5 (CH), 128.2 (CH), 127.4 (C), 127.0 (C), 125.7 (CH), 121.9 (CH), 121.9 (CH), 121.6 (CH), 121.5 (CH), 121.2 (2 × C), 119.8 (CH), 119.6 (CH), 119.2 (CH), 119.2 (CH), 111.3 (CH), 111.1 (CH), 44.1 (CH_2), 42.6 (CH_2), 33.2 (CH), 31.6 (CH), 20.3 (CH_3). Found (EI) $[M]^+$ 387.2090, $C_{27}H_{26}N_2$ requires 378.2091.

3,3'-(3-Phenylbutane-1,1-diyl)bis(1H-indole) **124k:**



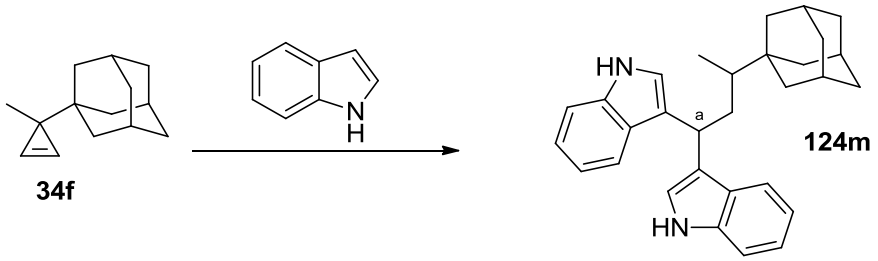
Purified using a gradient eluent system of 7:1 → 2:1 hexane:diethyl ether. Pale yellow oil obtained. R_f 0.12 (2:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3412 m (N-H), 2957 m 2925 m 2867 w (C-H), 1492 w 1455 s (Ar C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1H, NH), 7.76 (s, 1H, NH), 7.58 (d, *J* = 7.9 Hz, 1H, Ar-H), 7.43 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.38 – 6.90 (m, 13H, Ar-H), 4.38 (dd, *J* = 8.5, 6.7 Hz, 1H, H_a), 2.87 – 2.71 (m, 1H, CH_3CH), 2.62 – 2.41 (m, 2H, $CHCH_2CH$), 1.33 (d, *J* = 6.9 Hz, 3H, $CHCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7 (C), 136.8 (C), 136.7 (C), 128.5 (CH), 127.5 (CH), 127.2 (C), 127.1 (C), 126.1 (CH), 121.9 (2 × CH), 121.8 (CH), 121.5 (CH), 120.7 (C), 120.0 (CH), 119.7 (C), 119.5 (CH), 119.2 (CH), 119.1 (CH), 111.2 (CH), 111.2 (CH), 44.5 (CH_2), 38.0 (CH), 31.9 (CH), 22.8 (CH_3). Found (EI) $[M]^+$ 364.1935, $C_{26}H_{24}N_2$ requires 364.1934.

3,3'-(3-Cyclohexylbutane-1,1-diyl)bis(1H-indole) **124l:**



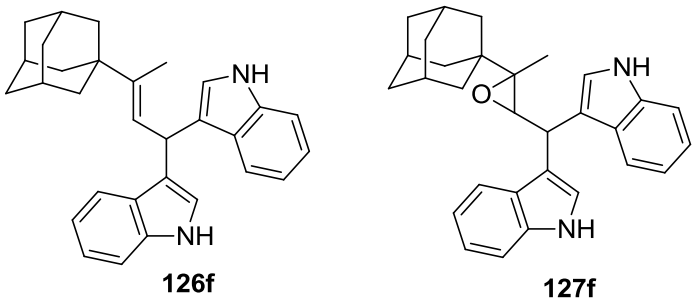
Purified using an eluent system of 2:1 hexane:diethyl ether. White film obtained. R_f 0.14 (2:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3411 m (N-H), 2921 m 2850 w (C-H), 1455 m (Ar C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H, N<u>H</u>), 7.79 (s, 1H, N<u>H</u>), 7.67 (d, *J* = 7.9 Hz, 1H, Ar-H), 7.61 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.33 (m, 2H, Ar-H), 7.23 – 6.97 (m, 5H, Ar-H), 6.87 (m, 1H, Ar-H), 4.61 (dd, *J* = 9.9, 5.4 Hz, 1H, H_a), 2.31 (ddd, *J* = 13.9, 9.9, 4.3 Hz, 1H, CHC<u>H</u>HCH), 1.98 (ddd, *J* = 13.6, 9.3, 5.4 Hz, 1H, CHCH<u>H</u>CH), 1.81 – 1.00 (m, 12H), 0.98 (d, *J* = 6.8 Hz, 3H, CHC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.74 (C), 136.7 (C), 127.5 (C), 127.1 (C), 121.9 (2 × CH), 121.8 (C), 121.6 (CH), 121.5 (CH), 119.9 (CH), 119.8 (C), 119.6 (CH), 119.1 (2 × CH), 111.2 (CH), 111.15 (CH), 43.4 (CH), 40.4 (CH_2), 35.8 (CH), 31.7 (CH), 30.6 (CH_2), 28.9 (CH_2), 27.1 (CH_2), 16.4 (CH_3). Found (APCI) $[M]^+$ 370.2406, $C_{26}H_{30}N_2$ requires 370.2404.

3,3'-(3-(Adamantan-1-yl)butane-1,1-diyl)bis(1H-indole) **124m:**

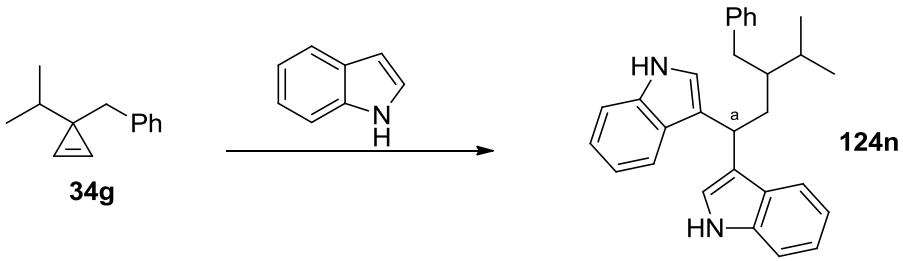


Purified using a gradient eluent system of 8:1 → 3:1 hexane:diethyl ether. White film obtained. R_f 0.17 (2:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3414 m (N-H), 2901 s 2847 m (C-H), 1455 (Ar C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 1H, NH), 7.75 (s, 1H, NH), 7.70 (d, *J* = 7.4 Hz, 1H, Ar-H), 7.60 (d, *J* = 7.7 Hz, 1H, Ar-H), 7.40 – 7.26 (m, 2H, Ar-H), 7.23 – 6.98 (m, 5H, Ar-H), 6.79 (d, *J* = 2.3 Hz, 1H, Ar-H), 4.61 (dd, *J* = 11.5, 3.6 Hz, 1H, H_a), 2.55 – 2.36 (m, 1H, CHCHH'CH), 1.92 (s, 3H, adamantyl H), 1.87 – 1.76 (m, 1H, CHCHH'CH), 1.75 – 1.08 (m, 13H, alkyl H), 1.01 (d, *J* = 6.6 Hz, 3H, $CHCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.8 (C), 136.7 (C), 127.7 (C), 127.0 (C), 122.5 (C), 121.9 (CH), 121.8 (CH), 121.76 (CH), 121.6 (CH), 120.1 (CH), 119.5 (CH), 119.2 (CH), 119.1 (CH), 119.07 (C), 111.3 (CH), 111.1 (CH), 40.7 (CH), 39.5 (CH_2), 37.6 (CH_2), 36.6 (CH_2), 35.0 (C), 32.0 (CH), 28.9 (CH), 13.1 (CH_3). Found (EI) $[M]^+$ 422.2711, $C_{30}H_{34}N_2$ requires 422.2171.

The alkene **126f** and epoxide **127f** were also observed as minor side-products in this reaction (4% and 2% respectively). See pages 110 and 111 for characterisation of **126f** and **127f** respectively.

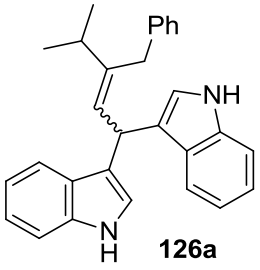


3,3'-(3-Benzyl-4-methylpentane-1,1-diyl)bis(1H-indole) **124n:**

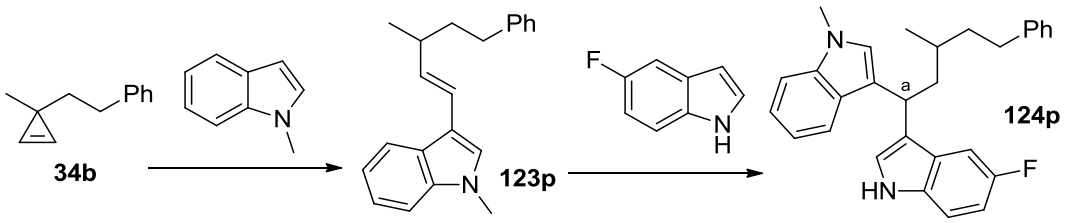


Gold(I) catalyst and solvent were added under a nitrogen atmosphere (glovebox). The reaction vessel was sealed and removed from the glovebox, and the reaction was allowed to stir at 40 ^{o}C for 48 h. Purified using a gradient eluent system of 7:1 → 2:1 hexane:diethyl ether. White film obtained. R_f 0.15 (2:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3413 m (N-H), 2957 m 2930 m (C-H), 1455 m (Ar C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (s, 1H, N<u>H</u>), 7.76 (s, 1H, N<u>H</u>), 7.64 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.47 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.39 – 6.95 (m, 11H, Ar-H), 6.82 (d, *J* = 2.3 Hz, 1H, Ar-H), 6.54 (d, *J* = 2.2 Hz, 1H, Ar-H), 4.58 (t, *J* = 7.7 Hz, 1H, <u>H$_a$</u>), 2.67 (dd, *J* = 13.4, 6.5 Hz, 1H, CH<u>H</u>Ph), 2.57 (dd, *J* = 13.4, 7.9 Hz, 1H, C<u>H</u>HPh), 2.30 – 2.16 (m, 1H, CH$_a$C<u>H</u>H), 2.05 (ddd, *J* = 14.0, 8.0, 6.4 Hz, 1H, CH$_a$CH<u>H</u>), 1.90 (dq, *J* = 6.9, 2.7 Hz, 1H, CH_2C<u>H</u>CH_2), 1.78 – 1.64 (m, 1H, CH_3C<u>H</u>CH_3), 0.92 (d, *J* = 6.9 Hz, 3H, CHC<u>H$_3$</u>), 0.89 (d, *J* = 6.9 Hz, 3H, CHC<u>H$_3$</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.3 (C), 136.8 (C), 136.6 (C), 129.5 (CH), 128.2 (CH), 127.4 (C), 127.1 (C), 125.6 (CH), 121.9 (CH), 121.8 (CH), 121.8 (CH), 121.5 (C), 120.7 (C), 120.2 (CH), 119.7 (2 × CH), 119.2 (CH), 119.1 (CH), 111.2 (CH), 111.0 (CH), 43.7 (CH), 37.0 (CH_2), 36.2 (CH_2), 31.7 (CH), 28.7 (CH), 19.1 (CH_3), 18.8 (CH_3). Found (APCI) $[M]^+$ 406.2399, $C_{29}H_{30}N_2$ requires 406.2404.

Note: Following the general synthetic procedure as described on page 95, alkene **126a** was also observed as a minor side-product in this reaction. NMR analysis of the crude reaction mixture indicated that **124n** and **126a** were produced in 21% and 14% yields respectively. These two products are inseparable; therefore the above procedure was followed as an alternative, to avoid alkene formation. See page 112 for characterisation of **126a**.



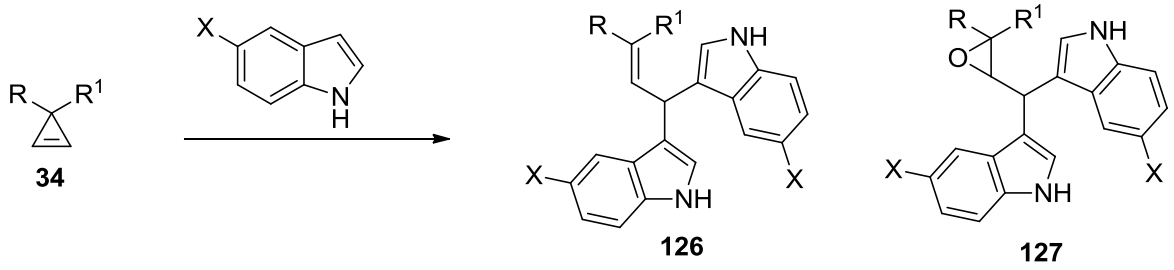
5-Fluoro-3-(3-methyl-1-(1-methyl-1H-indol-3-yl)-5-phenylpentyl)-1H-indole **124p**:



To a 0.139 M dichloromethane solution of cyclopropene **34b** (20.0 mg, 0.126 mmol) and 1-methylindole (11.4 mg, 0.087 mmol), 5 mol% of catalyst **1** (3.1 mg, 0.004 mmol) was added. The reaction was allowed to stir for 3 h, followed by addition of 5-fluoroindole (23.0 mg, 0.170 mmol). A reflux condenser was then attached, and the reaction was left to stir overnight at reflux. The solution was filtered through a silica plug with diethyl ether and 2% NEt_3, followed by concentration under reduced pressure. The crude reaction mixture was then purified using flash column chromatography (gradient eluent system of 5:1 → 2:1 hexane:diethyl ether). A mixture of two diastereoisomers **124p** was obtained as a colourless oil (14.2 mg, 0.033 mmol, 38%).

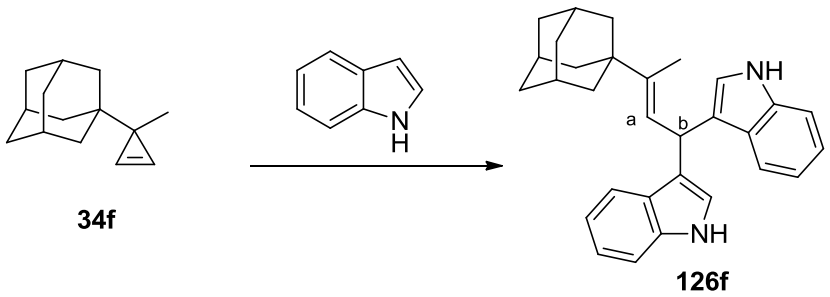
R_f 0.35 (2:1 hexane:diethyl ether). ν_{max}/cm^{-1} 3420 m (N-H), 2925 m 2854 w (C-H), 1483 m 1453 m (Ar C=C) 1093 m (C-F); ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H, NH/NH'), 7.85 (s, 1H, NH/NH'), 7.62 – 7.54 (m, 2H, Ar-H), 7.29 – 6.76 (m, 26H, Ar-H), 4.53 (dd, *J* = 8.0, 7.4 Hz, 2H, H_aH_a'), 3.72 (s, 3H, NCH_3/NCH_3'), 3.70 (s, 3H, NCH_3/NCH_3'), 2.67 – 2.48 (m, 4H), 2.34 – 2.21 (m, 2H), 2.09 – 1.96 (m, 2H), 1.81 – 1.68 (m, 2H), 1.62 – 1.49 (m, 4H), 1.06 (2 × d, *J* = 6.3 Hz, 6H, $CHCH_3$/ $CHCH_3$'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6 (d, *J* = 233.7 Hz, 2 × C-F/C-F'), 143.2 (2 × C/C'), 137.5 (2 × C/C'), 133.2 (2 × C/C'), 128.5 (2 × CH/CH'), 128.4 (2 × CH/CH'), 126.30 (2 × C/C'), 126.3 (d, *J* = 8.8 Hz, 2 × CH/CH'), 125.6 (2 × CH/CH'), 123.3 (2 × CH/CH'), 121.5 (2 × CH/CH'), 120.26 (2 × C/C'), 119.7 (d, *J* = 19.4 Hz, 2 × CH/CH'), 119.1 (2 × C/C'), 118.6 (2 × CH/CH'), 118.0 (2 × C/C'), 110.2 (d, *J* = 26.4, 2 × CH/CH'), 109.3 (2 × CH/CH'), 104.8 (d, *J* = 23.4 Hz, 2 × CH/CH'), 104.6 (d, *J* = 23.4 Hz, 2 × CH/CH'), 43.2 (CH_2/CH_2'), 43.1 (CH_2/CH_2'), 39.3 (CH_2/CH_2'), 39.2 (CH_2/CH_2'), 33.42 (CH_2/CH_2'), 33.38 (CH_2/CH_2'), 32.82 (CH_3/CH_3'), 32.78 (CH_3/CH_3'), 31.6 (2 × CH/CH'), 30.5 (CH/CH'), 30.4 (CH/CH'), 20.1 (2 × CH_3/CH_3'). Found (ESI) $[M+Na]^+$ 447.2201, $C_{29}H_{29}FN_2Na$ requires 447.2201.

***Bis*-indolylalkene 126 and epoxide 127 general synthetic procedure:**



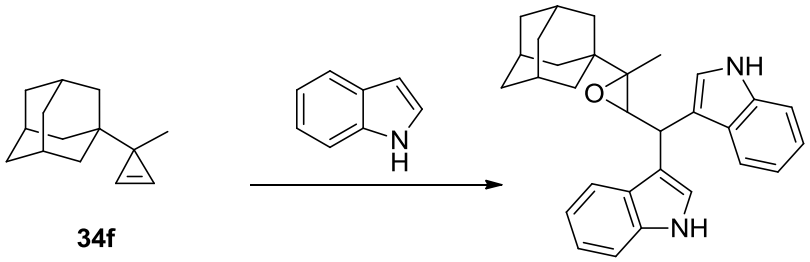
PPh_3AuNTf_2 (2:1 toluene adduct, 4.5 mg, 5.7×10^{-6} mol) was added to a stirring solution of **34e** (23.3 mg, 0.114 mmol) and 5-methoxyindole (34.0 mg, 0.231 mmol) in DCM (0.139 M). The resulting solution was allowed to stir overnight at r.t. (either with an O_2 balloon, or in a stoppered flask). The crude material was concentrated under reduced pressure, and the products were isolated by flash column chromatography.

(*E*)-3,3'-(3-(Adamantan-1-yl)but-2-ene-1,1-diyl)*bis*(1H-indole) **126f:**



Attempts to purify this compound were unsuccessful due to contamination from *bis*-indolylalkane **124n**. ^{1}H NMR analysis of characteristic alkene peaks, along with HRMS data confirmed formation of the *bis*-indolylalkene product. An NMR yield of 6% was determined by comparison to an internal standard (dimethyl sulfone). Characteristic alkene peaks: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (dd, J = 8.9, 1.3 Hz, 1H, H_a), 5.38 (d, J = 8.9 Hz, 1H, H_b). Found (EI) $[M]^+$ 420.2557, $C_{30}H_{32}N_2$ requires 420.2560.

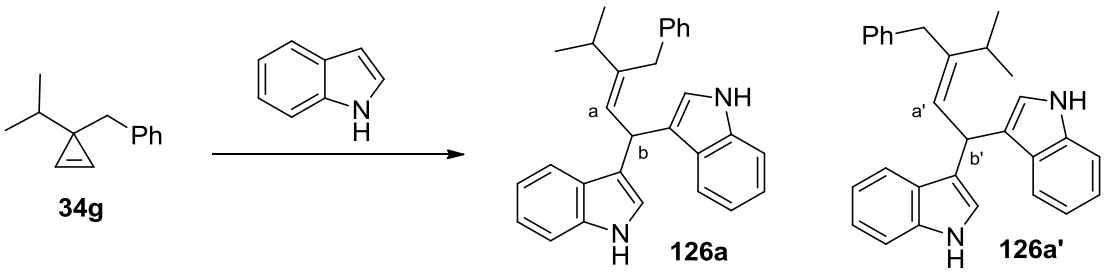
3,3'-((3-(Adamantan-1-yl)-3-methyloxiran-2-yl)methylene)*bis*(1H-indole) **127f:**



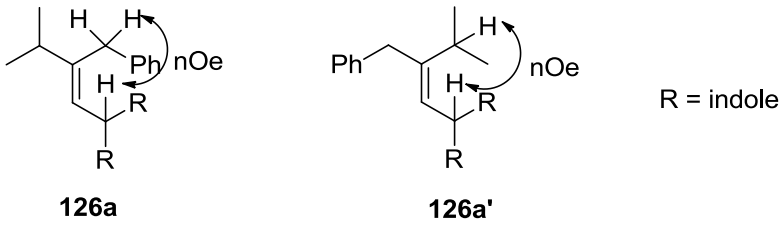
34f **127f**

Purified using a gradient eluent system of 8:1 → 2:1 hexane:diethyl ether. White film obtained. R_f 0.15 (2:1 hexane:diethyl ether), ν_{max}/cm^{-1} 3413 m (N-H), 2902 s 2848 m (C-H), 1455 (Ar C=C), 1091 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (s, 1H, N<u>H</u>), 7.93 (s, 1H, N<u>H</u>), 7.68 (d, *J* = 7.7 Hz, 1H, Ar-H), 7.48 – 7.29 (m, 3H, Ar-H), 7.23 – 6.89 (m, 6H, Ar-H), 4.43 (d, *J* = 9.0 Hz, 1H, C(O)CHC<u>H</u>), 3.71 (d, *J* = 9.0 Hz, 1H, C(O)C<u>H</u>CH), 1.96 (s, 3H, adamantyl H), 1.76 – 1.48 (m, 12H, adamantyl H), 1.37 (s, 3H, CC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.8 (C), 136.5 (C), 127.4 (C), 127.0 (C), 122.4 (CH), 122.2 (CH), 122.0 (CH), 121.4 (CH), 120.4 (CH), 120.1 (CH), 119.5 (CH), 119.4 (CH), 118.5 (C), 116.4 (C), 111.2 (CH), 111.0 (CH), 66.6 (C), 63.3 (CH), 37.8 (CH_2), 37.1 (CH_2), 36.0 (C), 34.8 (CH), 28.5 (CH), 13.7 (CH_3). Found (EI) $[M]^+$ 436.2509, $C_{30}H_{32}N_2O$ requires 436.2509.

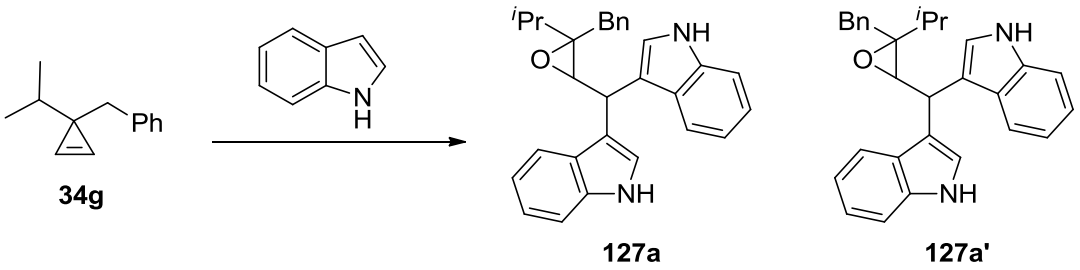
3,3'-(3-Benzyl-4-methylpent-2-ene-1,1-diyl)*bis*(1H-indole) **126a**/**126a':**



Purified using a gradient eluent system of 5:1 → 2:1 hexane:diethyl ether. Thin white film obtained as *E*-/*Z*- mixture of isomers (1.9:1 ratio). R_f 0.15 (2:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3414 s (N-H), 3058 w 2959 m 2926 m (C-H), 1640 w (C=C), 1493 w 1455 s (Ar C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 2H, NH/NH'), 7.87 (s, 2H, NH/NH'), 7.55 – 6.76 (m, 30H, indole & Ar H/H'), 6.02 (d, *J* = 9.3 Hz, 1H, C=CHCH), 5.56 (d, *J* = 9.7 Hz, 1H, C=CHCH'), 5.52 (d, *J* = 9.3 Hz, 1H, C=CHCH'), 5.45 (d, *J* = 9.3 Hz, 1H, C=CHCH), 3.69 (s, 2H, CH_2Ph), 3.39 (s, 2H, CH_2Ph'), 3.32 – 3.23 (m, 1H, CH_3CHCH_3'), 2.32 – 2.22 (m, 1H, CH_3CHCH_3), 1.02 (t, *J* = 6.6 Hz, 12H, 2 × CH_3/2 × CH_3'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.4 (C), 143.3 (C), 141.5 (C), 140.6 (C), 136.9 (C), 136.8 (C), 130.2 (CH), 129.5 (CH), 129.0 (CH), 128.3(CH), 128.2 (CH), 127.24 (C), 127.18 (CH), 125.83 (CH), 125.80 (CH), 122.2 (CH), 122.1 (CH), 121.9 (CH), 120.3 (CH), 120.2 (CH), 120.1 (C), 120.0 (C), 119.2 (CH), 119.1 (CH), 111.1 (CH), 38.4 (CH_2), 35.8 (CH_2), 33.7 (CH), 33.4 (CH), 32.6 (CH), 29.6 (CH), 22.4 (CH_3), 21.6 (CH_3). Found (APCI) $[M-H]^+$ 403.2168, $C_{29}H_{27}N_2$ requires 403.2169.

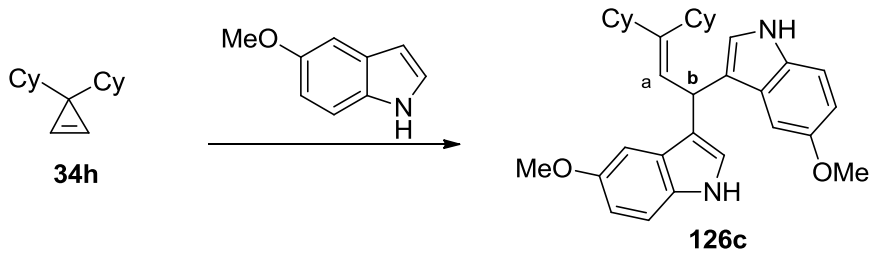


3,3'-((3-Benzyl-3-isopropyloxiran-2-yl)methylene)*bis*(1H-indole) **127a**/**127a':**



Purified using a gradient eluent system of 5:1 → 2:1 hexane:diethyl ether. Thin white film obtained as mixture of diastereoisomers in 1.3:1 ratio. R_f 0.07 (2:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3412 m (N-H), 3059 w 2964 m (C-H), 1495 w 1456 m (Ar C=C); ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (s, 1H, NH), 8.03 (s, 1H, NH'), 7.92 (s, 1H, NH), 7.80 (s, 1H, NH'), 7.71 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.60 (d, *J* = 8.0 Hz, 1H, Ar-H'), 7.49 (d, *J* = 7.7 Hz, 1H, Ar-H), 7.44 – 6.75 (m, 27H, indole and benzene ring H), 4.60 (d, *J* = 9.0 Hz, 1H, C(O)CHCH), 4.49 (d, *J* = 9.6 Hz, 1H, C(O) CHCH'), 3.59 (d, *J* = 9.1 Hz, 1H, C(O)CH'CH), 3.26 (d, *J* = 9.6 Hz, 1H, C(O)CHCH), 3.13 (d, *J* = 14.9 Hz, 1H, CHHPh), 3.03 (d, *J* = 15.0 Hz, 1H, CHHPh), 2.96 (s, 2H, CH_2'Ph), 2.21 – 2.08 (m, 1H, $CH(CH_3)_2$), 1.93 – 1.81 (m, 1H, $CH'(CH_3)_2$), 1.19 (d, *J* = 6.8 Hz, 3H, CH_3CHCH_3), 0.84 (d, *J* = 6.8 Hz, 3H, $CH_3'CHCH_3$), 0.80 – 0.71 (m, 6H, CH_3CHCH_3 & CH_3CHCH_3'); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3 (C), 136.9 (C), 136.8 (C), 136.6 (C), 136.5 (C), 136.4 (C), 130.5 (CH), 130.0 (CH), 128.4 (CH), 128.1 (CH), 127.4 (C), 127.3 (C), 127.0 (C), 126.9 (C), 126.4 (CH), 122.5 (CH), 122.3 (CH), 122.23 (CH), 122.20 (CH), 122.1 (CH), 122.0 (CH), 121.6 (CH), 121.5 (CH), 121.4 (CH), 120.6 (CH), 120.5 (CH), 120.3 (CH), 120.2 (CH), 120.1 (CH), 119.6 (CH), 119.5 (CH), 119.4 (CH), 118.4 (C), 118.3 (C), 116.5 (C), 116.1 (C), 111.3 (CH), 111.2 (CH), 111.1 (CH), 111.0 (CH), 67.1 (C), 67.0 (C), 66.0 (CH), 63.4 (CH), 35.8 (CH_2), 35.2 (CH_2), 34.7 (CH), 33.7 (CH), 31.4 (CH), 30.8 (CH), 19.5 (CH_3), 18.4 (CH_3). Found (APCI) $[M]^+$ 420.2193, $C_{29}H_{28}N_2O$ requires 420.2196.

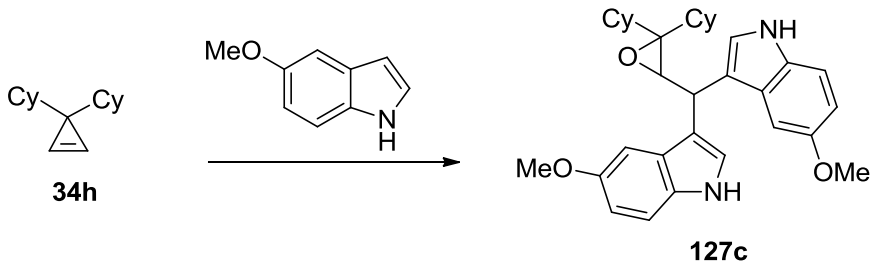
3,3'-(3,3-Dicyclohexylprop-2-ene-1,1-diyl)*bis*(5-methoxy-1H-indole) **126c**:



34h **126c**

Purified using a gradient eluent system of 4:1 → 1:1 hexane:diethyl ether. Thin white film obtained. R_f 0.13 (2:1 hexane:diethyl ether); ν_{max}/cm^{-1} 2413 m (N-H), 2923 s 2850 m (C-H), 1623 m (C=C), 1456 m (Ar C=C); ^{1}H NMR (400 MHz,$CDCl_3$), δ 7.77 (2H, br s, N-H), 7.24 (2H, d, *J* = 8.8 Hz, Ar-H), 7.00 (2H, d, *J* = 2.2 Hz, Ar-H), 6.85 – 6.81 (4H, m, Ar-H), 5.67 (1H, d, *J* = 9.20 Hz, H_a), 5.39 (1H, d, *J* = 9.20 Hz, H_b), 3.75 (6H, s, OMe), 2.77 (1H, tt, *J* = 11.8, 4.8 Hz, C<u>H</u>$(CH_2)_2$), 1.99 (1H, m, C<u>H</u>$(CH_2)_2$), 1.72 – 1.00 (20H, m, Cy-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5 (C), 149.5 (C), 131.9 (C), 127.6 (C), (plus an overlapping peak), 126.0 (CH), 123.0 (2 × CH), 119.9 (C), 112.0 (2 × CH), 111.7 (2 × CH), 102.0 (2 × CH), 55.8 (2 × CH_3), 40.9 (CH), 40.0 (CH), 35.3 (CH_2), 32.2 (CH), 31.0 (CH_2), 27.2 (CH_2), 26.6 (CH_2), 26.3 (CH_2), 26.2 (CH_2). Found (EI) $[M]^+$ 496.3084, $C_{33}H_{40}N_2O_2$ requires 496.3084.

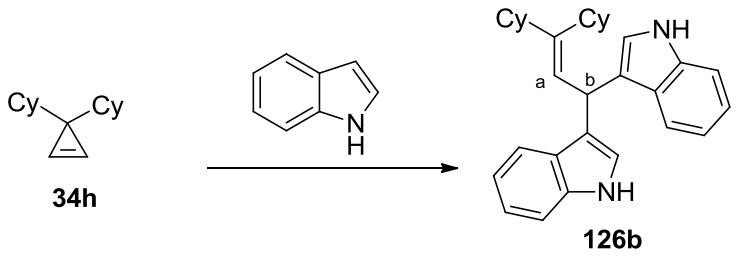
3,3'-((3,3-Dicyclohexyloxiran-2-yl)methylene)*bis*(5-methoxy-1H-indole) **127c**:



34h **127c**

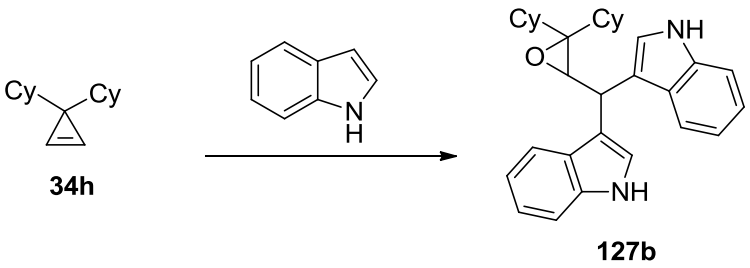
Purified using a gradient eluent system of 4:1 → 1:1 hexane:diethyl ether. Thin white film obtained. R_f 0.06 (2:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3410 m (N-H), 2926 s 2852 m (C-H), 1583 w 1484 m 1451 m (Ar C=C) 1260 m (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (s, 1H, NH), 7.84 (s, 1H, NH), 7.24-7.10 (m, 4H, Ar-H), 6.99 (dd, *J* = 13.8, 2.2 Hz, 2H, Ar-H), 6.85-6.76 (m, 2H, Ar-H), 4.44 (d, *J* = 9.1 Hz, 1H, C(O)CHCH), 3.73 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.63 (d, *J* = 9.1 Hz, 1H, C(O)CHCH), 1.96 – 0.83 (m, 22H, Cy-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9 (C), 153.7 (C), 132.0 (C), 131.3 (C), 127.8 (C), 127.6 (C), 122.9 (CH), 122.3 (CH), 118.6 (C), 116.5 (C), 112.4 (CH), 112.0 (CH), 111.9 (CH), 111.6 (CH), 102.5 (CH), 101.5 (CH), 69.2 (C), 65.2 (CH), 56.0 (CH_3), 55.7 (CH_3), 42.9 (CH), 37.9 (CH), 33.7 (CH), 32.5 (CH_2), 29.4 (CH_2), 28.3 (CH_2), 28.0 (CH_2), 26.6 (4 × CH_2), 26.5 (2 × CH_2). Found (ESI) $[M+H]^+$ 513.3107, $C_{33}H_{41}N_2O_3$ requires 513.3112.

3,3'-(3,3-Dicyclohexylprop-2-ene-1,1-diyl)*bis*(1H-indole) **126b:**



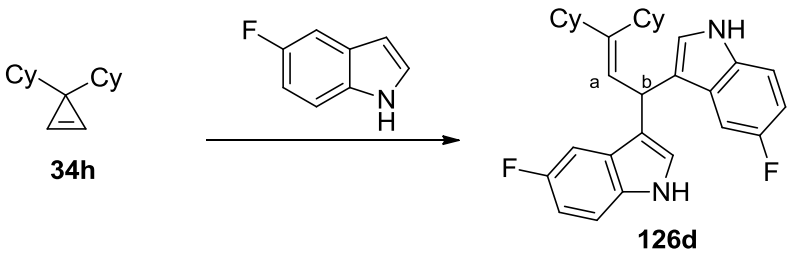
Purified using a gradient eluent system of 3:1 → 1:1 hexane:diethyl ether. Thin white film obtained. R_f 0.23 (2:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3412 m (N-H), 2923 s 2850 m (C-H), 1617 w (C=C), 1455 m (Ar C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 2H, 2 × N<u>H</u>), 7.53 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.35 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.23 – 7.11 (m, 2H, Ar-H), 7.08 – 6.96 (m, 2H, Ar-H), 6.85 (d, *J* = 1.6 Hz, 2H Ar-H), 5.66 (d, *J* = 9.1 Hz, 1H, H_a), 5.48 (d, *J* = 9.1 Hz, 1H, H_b), 2.76 (tt, *J* = 11.7, 3.6 Hz,1H, C<u>H</u>$(CH_2)_2$), 1.98 (t, *J* = 9.8 Hz, 1H, C<u>H</u>$(CH_2)_2$), 1.85 – 0.99 (m, 20H, Cy-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5 (C), 136.8 (2 × C), 127.3 (2 × C), 126.0 (CH), 122.2 (2 × CH), 121.8 (2 × CH), 120.5 (2 × C), 120.4 (2 × CH), 119.0 (2 × CH), 111.1 (2 × CH), 41.0 (CH), 40.1 (CH), 35.4 (CH_2), 32.3 (CH), 31.1 (CH_2), 27.4 (CH_2), 26.8 (CH_2), 26.5 (CH_2), 26.4 (CH_2). Found (EI) $[M-H]^+$ 435.2081, $C_{31}H_{35}N_2$ requires 435.2795.

3,3'-((3,3-Dicyclohexyloxiran-2-yl)methylene)*bis*(1H-indole) **127b:**



Purified using an eluent system of 4:1 hexane:diethyl ether. Blue oil obtained. R_f 0.13 (2:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3411 m (N-H), 2926 s 2852 m (C-H), 1455 m (Ar C=C), 1095 w (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H, NH), 7.91 (s, 1H, NH), 7.64 (dd, *J* = 8.0, 1.1 Hz, 1H, Ar-H), 7.51 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar-H), 7.36 (dt, *J* = 8.2, 0.9 Hz, 1H, Ar-H), 7.30 (dt, *J* = 8.1, 0.9 Hz, 1H, Ar-H), 7.21 – 6.99 (m, 6H, Ar-H), 4.54 (d, *J* = 9.2 Hz, 1H, C(O)CHCH), 3.64 (d, *J* = 9.2 Hz, 1H, C(O)CHCH), 1.95 – 0.79 (m, 22H, Cy-H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.8 (C), 136.3 (C), 129.2 (CH), 128.4 (CH), 127.4 (C), 127.1 (C), 122.1 (CH), 122.0 (CH), 121.5 (CH), 120.4 (CH), 120.0 (CH), 119.5 (CH), 118.9 (C), 116.8 (C), 111.1 (CH), 111.0 (CH), 69.3 (C), 65.4 (CH), 42.8 (CH), 38.0 (CH), 33.9 (CH), 32.5 (CH_2), 29.5 (CH_2), 28.3 (CH_2), 28.0 (CH_2), 26.7 (CH_2), 26.6 (2 × CH_2), 26.57 (CH_2), 26.54 (CH_2), 26.50 (CH_2). Found (ESI) $[M+H]^+$ 453.2899, $C_{31}H_{37}N_2O$ requires 453.2900.

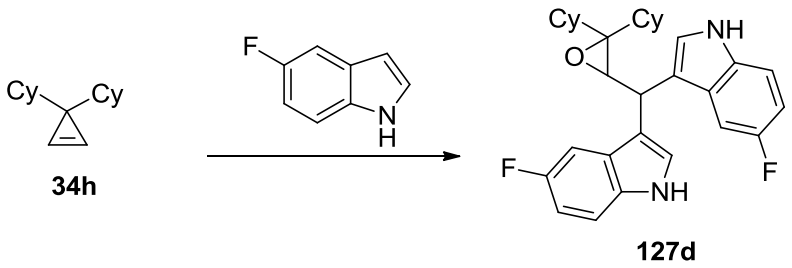
3,3'-(3,3-Dicyclohexylprop-2-ene-1,1-diyl)*bis*(5-fluoro-1H-indole) **126d:**



34h **126d**

Purified using a gradient eluent system of 3:1 → 1:1 hexane:diethyl ether. Thin white film obtained. R_f 0.23 (2:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3473 m 3429 m (N-H), 2924 s 2850 s (C-H), 1647 w (C=C), 1581 m 1483 s 1449 s (Ar C=C), 1091 m (C-F); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 2H, 2 × N<u>H</u>), 7.34 – 7.18 (m, 2H, Ar-H), 7.11 (dd, *J* = 10.0, 2.5 Hz, 2H, Ar-H), 6.97 – 6.81 (m, 4H, Ar-H), 5.60 (d, *J* = 9.1 Hz, 1H, H_a), 5.34 (d, *J* = 9.1 Hz, 1H, H_b), 2.70 (tt, *J* = 11.5, 3.5 Hz, 1H, C<u>H</u>$(CH_2)_2$), 1.98 (t, *J* = 10.1 Hz, 1H, C<u>H</u>$(CH_2)_2$), 1.89 – 1.00 (m, 20H, Cy-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5 (d, *J* = 233.8 Hz, 2 × C), 150.2 (C), 133.4 (2 × C), 127.5 (d, *J* = 9.8 Hz, 2 × C), 125.1 (CH), 123.9 (2 × CH), 120.2 (d, *J* = 4.7 Hz, 2 × C), 111.7 (d, *J* = 9.8 Hz, 2 × CH), 110.2 (d, *J* = 26.4 Hz, 2 × CH), 105.13 (d, *J* = 23.6 Hz, 2 × CH), 41.1 (CH), 40.1 (CH), 35.3 (CH_2), 32.4 (CH), 31.1 (CH_2), 27.3 (CH_2), 26.7 (CH_2), 26.4 (CH_2), 26.3 (CH_2). Found (EI) $[M]^+$ 472.2684, $C_{31}H_{34}N_2F_2$ 472.2685.

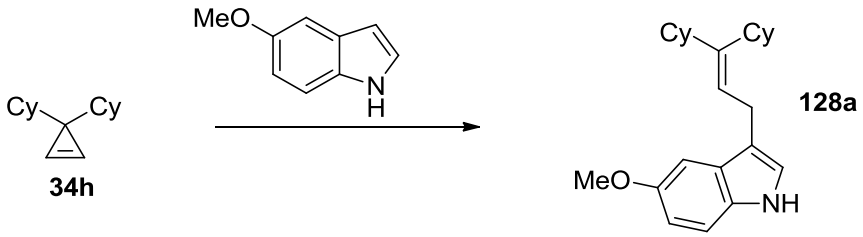
3,3'-((3,3-Dicyclohexyloxiran-2-yl)methylene)*bis*(5-fluoro-1H-indole) **127d:**



34h **127d**

Purified using a gradient eluent system of 4:1 → 1:1 hexane:diethyl ether. Thin white film obtained. R_f 0.09 (2:1 hexane:diethyl ether); ν_{max}/cm^{-1} 2470 w 3427 w (N-H), 2928 s 2853 m (C-H) 1582 w 1485 m 1452 m (Ar C=C), 1167 m (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (s, 1H, NH), 8.01 (s, 1H, NH), 7.30 – 7.04 (m, 6H, Ar-H), 6.94-6.83 (m, 2H, Ar-H), 4.38 (d, *J* = 9.3 Hz, 1H, C(O)CHCH), 3.59 (d, *J* = 9.3 Hz, 1H, C(O)CHCH), 1.94 – 0.76 (m, 22H, Cy-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7 (d, *J* = 233.9 Hz, 2 × C-F), 133.4 (C), 132.8 (C), 127.4 (2 × d, *J* = 9.9 Hz, 2 × C), 124.0 (CH), 123.2 (CH), 118.2 (d, *J* = 4.9 Hz, C), 116.4 (d, *J* = 4.8 Hz, C), 111.8 (2xd, *J* = 9.7 Hz, 2 × CH), 110.8 (d, *J* = 20.8 Hz, CH), 110.4 (d, *J* = 20.8 Hz, CH), 105.2 (d, *J* = 23.8 Hz, CH), 104.7 (d, *J* = 23.7 Hz, CH), 69.6 (C), 64.7 (CH), 42.7 (CH), 37.9 (CH), 33.9 (CH), 32.5 (CH_2), 29.5 (CH_2), 28.3 (CH_2), 27.9 (CH_2), 26.7 (CH_2), 26.6 (2 × CH_2), 26.5 (CH_2), 26.5 (CH_2), 26.4 (CH_2). Found (ESI) $[M+Na]^+$ 511.2525, $C_{31}H_{34}F_2N_2ONa$ requires 511.2531.

3-(3,3-Dicyclohexylallyl)-5-methoxy-1H-indole **128a:**

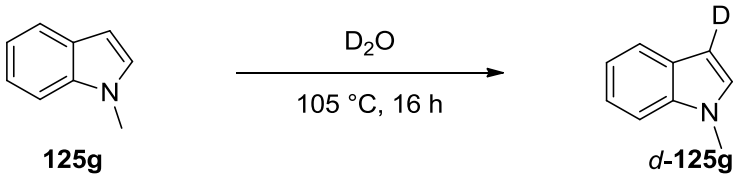


5-Methoxyindole (23.2 mg, 0.147 mmol) was added to **34h** (16.0 mg, 0.073 mmol) in a glass vial. The vial was flushed with nitrogen and then sealed; this was subsequently transferred to a glovebox under a nitrogen atmosphere. Under these oxygen- and moisture-free conditions, dry DCM was added, followed by PPh_3AuNTf_2 (2:1 toluene adduct, 3.4 mg, 4.6×10^{-3} mmol). The reaction was allowed to react in the glovebox overnight at room temperature, after which the vial was removed from the glovebox. The crude reaction mixture was flushed through a plug of silica using diethyl ether and 1% triethylamine, and concentrated under reduced pressure. The product was purified using flash column chromatography (10:1 → 1:1 hexane:diethyl ether), yielding **128a** as a pale yellow oil (12.1 mg, 0.034 mmol, 44%).

R_f 0.41 (2:1 hexane:diethyl ether); ν_{max}/cm^{-1} 3415 m (N-H), 2921 s 2849 s (C-H), 1624 (C=C), 1584 w 1484 s 1448 s (Ar C=C), 1214 (C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (s, 1H, NH), 7.24 (d, *J* = 8.8 Hz, 1H, CHCNH), 7.05 (d, *J* = 2.4 Hz, 1H, C(OMe)CHC), 6.91 (d, *J* = 2.2 Hz, 1H, CCHNH), 6.85 (dd, *J* = 8.8, 2.4 Hz, 1H, C(OMe)CHCH), 5.38 (t, *J* = 7.2 Hz, 1H, C=CHCH$_2$), 3.86 (s, 3H, OCH$_3$), 3.49 (d, *J* = 7.2 Hz, 2H, CHCH$_2$C), 2.59 (tt, *J* = 11.6, 3.5 Hz, 1H, CH(CH$_2$)$_2$), 1.94 (tt, *J* = 11.4, 3.1 Hz, 1H, CH(CH$_2$)$_2$), 1.87 – 0.99 (m, 20H, Cy-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9 (C), 150.8 (C), 131.8 (C), 128.0 (C), 122.2 (CH), 120.6 (CH), 116.5 (C), 112.3 (CH), 111.9 (CH), 101.0 (CH), 56.0 (CH_3), 40.8 (CH), 40.7 (CH), 35.2 (CH_2), 31.3 (CH_2), 27.4 (CH_2), 26.9 (CH_2), 26.5 (CH_2), 26.4 (CH_2), 23.6 (CH_2). Found (EI) $[M]^+$ 351.2560, $C_{24}H_{33}NO$ requires 351.2557.

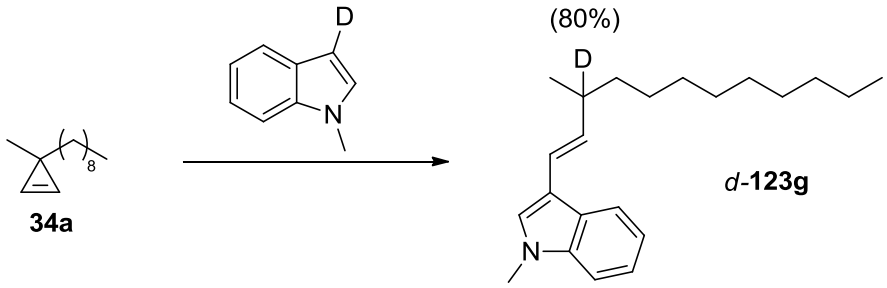
Deuterium labelling studies:

1-Methyl-3-deuteroindole *d*-**125g**:[48]



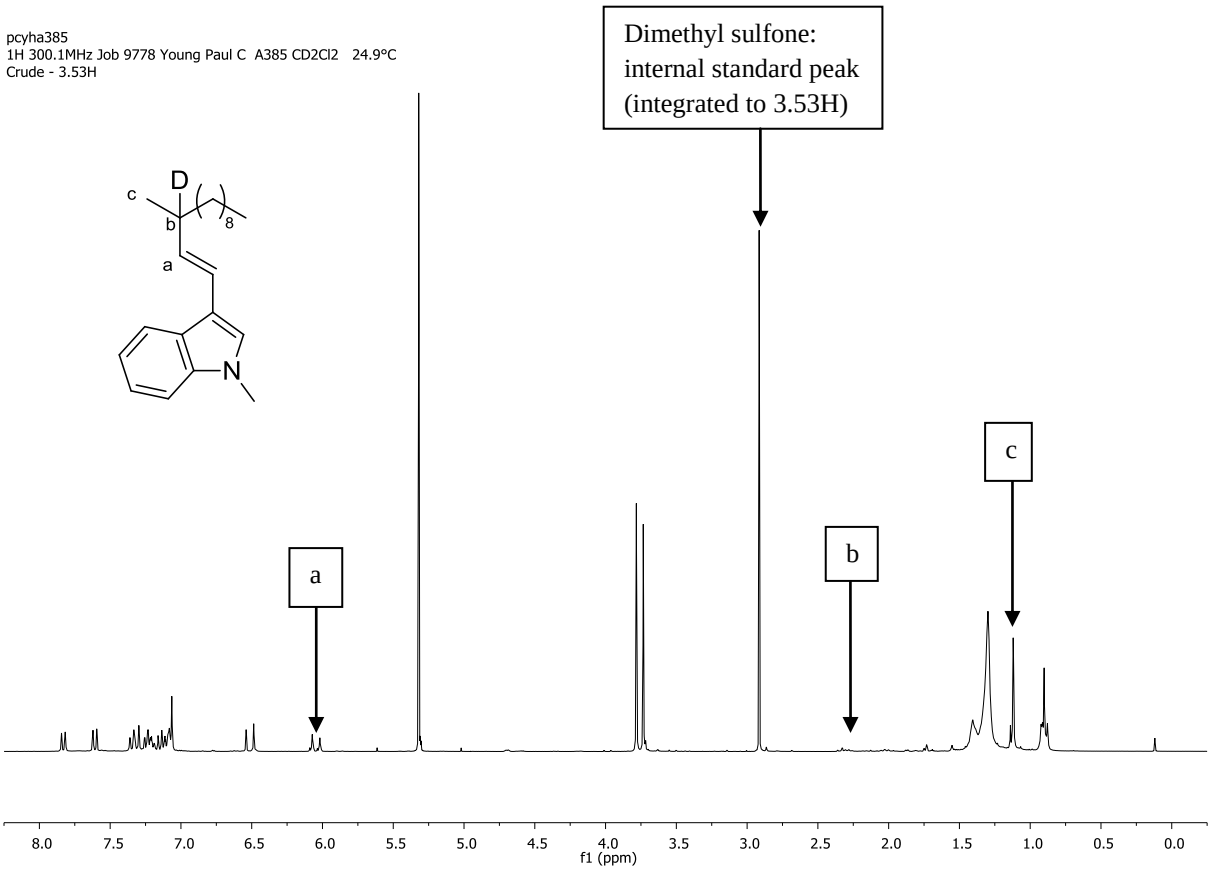
Argon-flushed 1-methylindole (0.5012 g, 3.82 mmol) was added to 1 mL D_2O. Reaction was heated to 105 °C and was allowed to react at reflux overnight, with vigorous stirring. The reaction was then cooled to room temperature and the product was extracted with hexane (3 × 5 mL), then dried over Na_2SO_4 and concentrated under reduced pressure. Analysis by ^1H NMR in $CDCl_3$ indicated that 1-methylindole was 94% deuterium-enriched at the C3 position.

(*E*)-N-Methyl-3-(3-deutero-3-methyl-dodec-1-en-1-yl)-1H-indole *d*-**123g**:

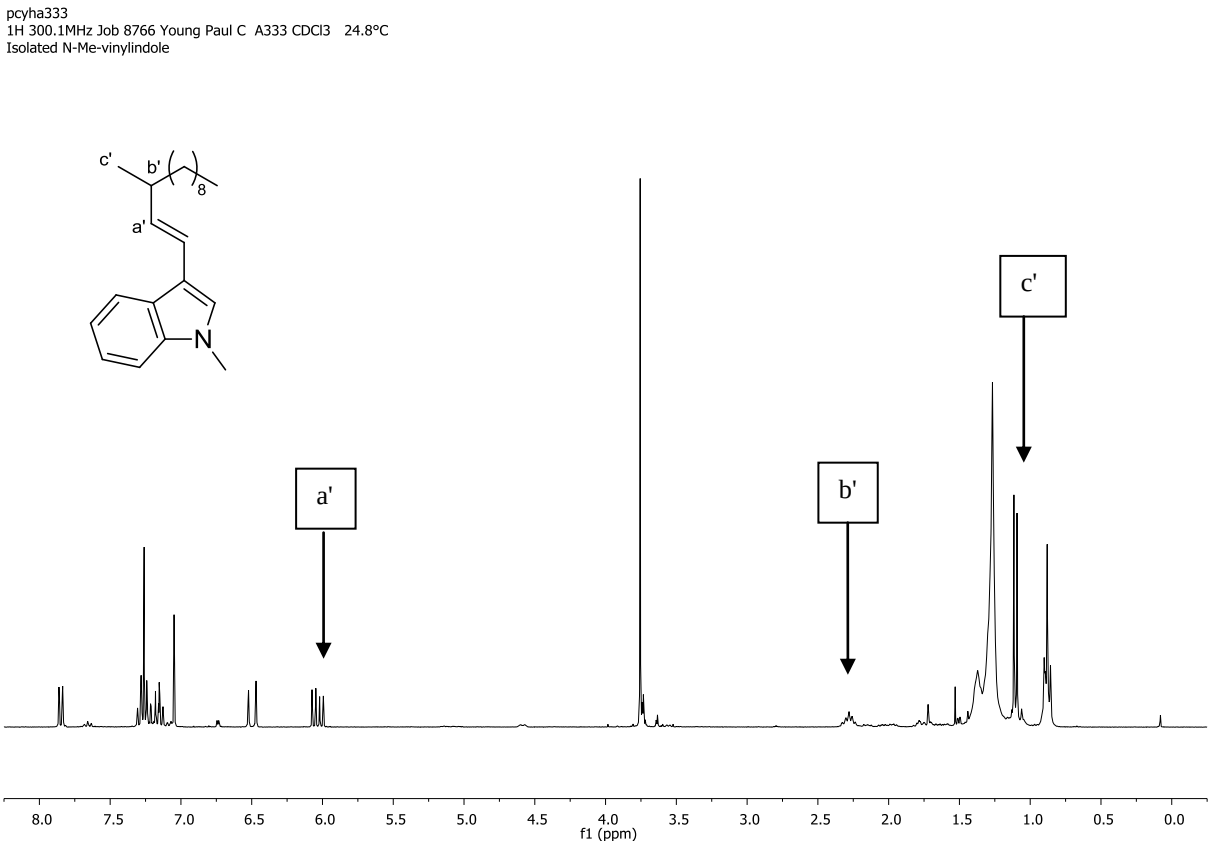


To a solution of 3-methyl-3-nonylcycloprop-1-ene **34a** (14.8 mg, 0.082 mmol) and 1-methyl-3-deuteroindole *d*-**125g** (21.9 mg, 0.166 mmol) in *d*-DCM (0.139 M), catalyst **1** (3.1 mg, 0.004 mmol) was added. The reaction was flushed with CaH_2-dried argon gas, and then allowed to stir for 3 h at 0 °C. The reaction was filtered through a silica plug, washed with diethyl ether and 2% triethylamine. The filtrate was concentrated under reduced pressure and dimethyl sulfone (4.5 mg, 0.048 mmol) was added as an internal standard for NMR analysis. Analysis of the ^1H NMR shows that *d*-**123g** formed in 89% yield, with 80% deuterium incorporation.

^{1}H NMR of the crude reaction mixture of *d*-**123g**:



^{1}H NMR of isolated **123g** for comparison:



Analysis of the ^{1}H NMR spectra of the crude reaction mixture demonstrated product *d*-**123g** had formed by the presence of characteristic peaks:

(a) δ 6.03 (d, *J* = 16.1 Hz, 1H, CDC<u>H</u>=CH). In **123g** this signal appears with dd multiplicity (a').

(b) Disappearance of a multiplet signal at δ 2.34 – 2.22 as this is the site of where deuteration takes place.

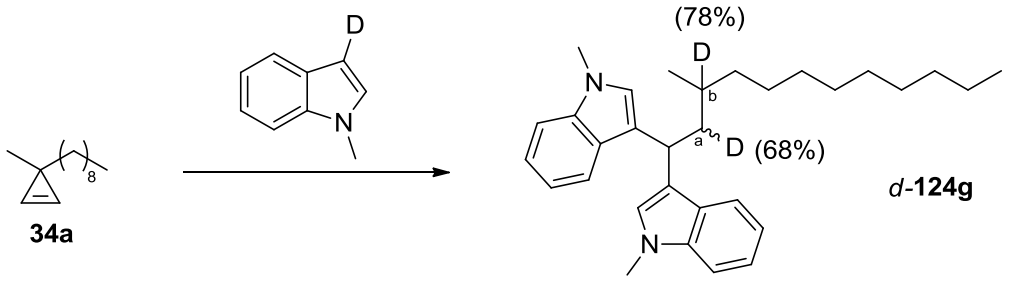
(c) δ 1.10 (s, 3H, C<u>H$_3$</u>CD). In **123g** this signal appears with d multiplicity (c').

Synthesis for isolation & characterisation of *d*-**123g**:

3-Methyl-3-nonylcycloprop-1-ene **34a** (27.3 mg, 0.151 mmol) and 1-methyl-3-deuteroindole *d*-**125g** (12.5 mg, 0.095 mmol) were added to a small vial. Under glovebox nitrogen conditions, 4Å MS-dried *d*-DCM (1 mL) and catalyst **1** (3.8 mg, 0.0049 mmol) were added to the vial, and the solution was allowed to stir for 4.5 h in the glovebox. The solution was then removed from the glovebox and concentrated under reduced pressure, and purification was attempted by flash column chromatography (40:1 hexane:diethyl ether), yielding a yellow oil. The resulting product was found to be highly unstable and repeated attempts at characterisation by ^{1}H NMR was unsuccessful due to rapid decomposition of the deuterated material. IR and HRMS data were obtained and supports *d*-**123g**, and the ^{1}H NMR of the crude mixture before attempted isolation also supports *d*-**123g** (as shown above).

R_f 0.55 (2:1 hexane:diethyl ether); ν_{max}/cm^{-1} 2923 s 2853 m (C-H), 2250 w (C-D), 1686 w (C=C), 1467 m (Ar C=C); Found (APCI) $[M+H]^+$ 313.2742, $C_{22}H_{33}DN$ requires 313.2749.

3,3'-(2,3-Dideutero-3-methyldodecane-1,1-diyl)*bis*(1-methyl-1H-indole) *d*-**124g:**



3-Methyl-3-nonylcycloprop-1-ene **34a** (15.4 mg, 0.085 mmol) and 1-methyl-3-deuteroindole *d*-**125g** (23.9 mg, 0.181 mmol) were added to a small vial. Under an inert atmosphere (glovebox), 4Å MS-dried *d*-DCM (0.6 mL) and catalyst **1** (3.2 mg, 0.0041 mmol) were added to the vial, the vial was then sealed and removed from the glovebox. The reaction was allowed to stir at 30 °C overnight in the sealed vial. The solution was then concentrated under reduced pressure, and purified by flash column chromatography (20:1 hexane:diethyl ether with 1% TEA), yielding a mixture of diastereoisomers as a colourless oil. ^{1}H NMR was carried out to determine the deuterium incorporation (68% at position a and 78% at position b).

R_f 0.35 (5:1 hexane:diethyl ether); ν_{max}/cm^{-1} 2922 s 2852 m (C-H), 2244 w (C-D), 1466 (Ar C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.61 (m, 2H, Ar-H), 7.31 – 7.24 (m, 2H, Ar-H), 7.23 – 7.16 (m, 2H, Ar-H), 7.10 – 7.02 (m, 2H, Ar-H), 6.88 (s, 1H, Ar-H), 6.78 (s, 1H, Ar-H), 4.66 – 4.57 (m, 1H, CHDC<u>H</u>), 3.74 (s, 3H, NC<u>H</u>$_3$), 3.69 (s, 3H, NC<u>H</u>$_3$'), 2.27 – 2.15 (m, 1H, C<u>H</u>D), 2.02 – 1.91 (m, 1H, CD<u>H</u>), 1.51 – 1.12 (m, 16H), 0.98 (d, *J* = 6.5 Hz, 3H, CHC<u>H</u>$_3$/CDC<u>H</u>$_3$), 0.89 (t, *J* = 6.9 Hz, 3H, CH_2C<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.4 (overlap 2 × C), 127.3 (C), 127.5 (C), 126.4 (CH), 126.3 (CH), 121.4 (overlap 2 × CH), 120.1 (C), 120.0 (CH), 119.8 (CH), 118.9 (C), 118.5 (overlap 2 × CH), 109.23 (CH), 109.20 (CH), 43.9 (CH_2), 43.5 (t, *J* = 17.6 Hz, CHD), 37.5 (CH_3), 37.4 (CH_3), 32.81 (CH), 32.75 (CH), 32.1 (CH_2), 31.4 (CH_2), 31.3 (CH_2), 30.7 (overlapping triplet, CD), 29.9 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 26.9 (CH_2), 22.9 (CH_2), 20.0 (CH_3), 14.3 (CH_3). HRMS not possible due to presence of *bis*-deuterated, *mono*-deuterated and non-deuterated products. ^{1}H, ^{2}H and ^{13}C isotope peaks all interfere with each signal, resulting in invalid HRMS values. Peak at 444.4 in LRMS (CI) demonstrates that expected product is present.

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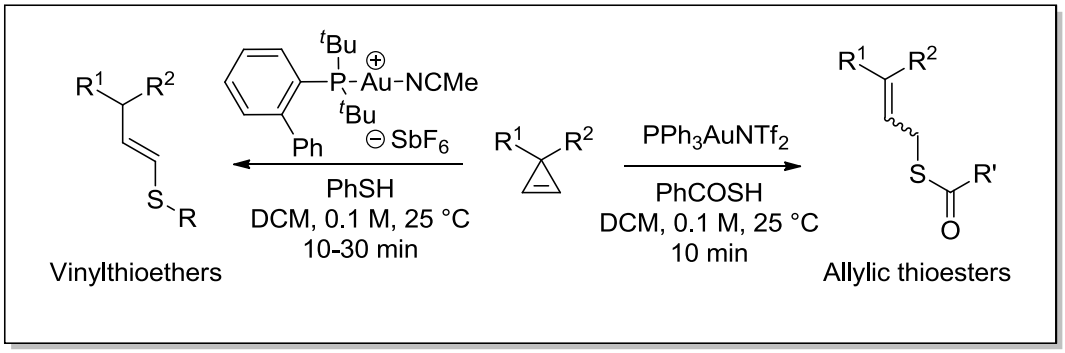
Chapter 3 – Gold(I)-Catalysed Addition of Thiols & Thioacids to 3,3-Disubstituted Cyclopropenes

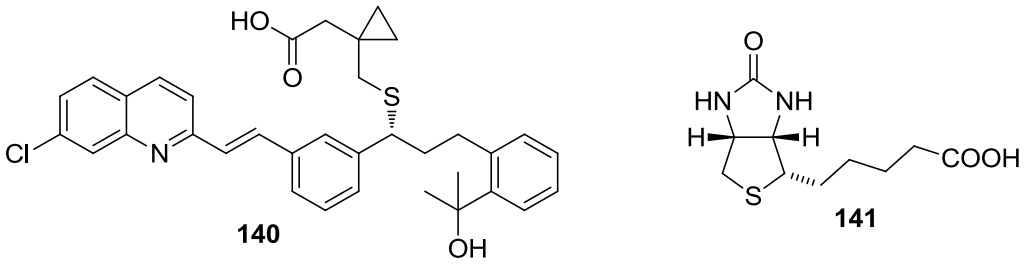


Acknowledgements: The author would like to thank Richard Mudd (MChem project student) for his input into this chapter. All work reported was carried out by the author, unless specifically stated otherwise. Table 3.1, entries 1, 2, 6 & 7 were completed by R. J. Mudd.

3.1 Introduction

Although there is a vast array of examples in the literature of gold(I)-catalysed additions of *O*-, *N*- and *C*-nucleophiles,[1-14] there are relatively few which have been shown to use sulfur-based nucleophiles.[15-26] Presumably, this can be attributed to the known strong coordination of sulfur to gold(I)-centres,[27, 28] as well as other late transition metal catalysts.[29]

Nevertheless, if nucleophilic sulfur-addition could occur, a number of valuable structure moieties are attainable. For example, thioethers are found in a wide variety of important pharmaceuticals and biologically active natural products (Figure 3.1).[30, 31] Montelukast **140** is a pharmaceutical drug used in the USA for the prevention of asthma attacks,[32] and vitamin B_7 **141** is a naturally occurring compound that helps the metabolism of proteins within the body.[33]



140 **141**

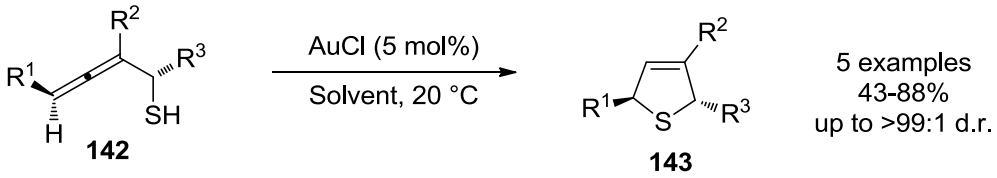
Figure 3.1. Examples of biologically important thioethers.

With such a large quantity of compounds that contain a thioether linkage, it is synthetically useful to have methods of installing such a group. The late transition metals do show a strong tendency to be poisoned by sulfur nucleophiles, rendering some catalysts inactive for reactions. However, more recently there have been increasingly more successful results in the literature which show that sulfur nucleophiles can achieve excellent yields and reaction outcomes.

3.1.1 Intramolecular Gold-Catalysed Reactions with Sulfur-Nucleophiles

Although there are few examples in which low-valent sulfur nucleophiles have been used successfully as a nucleophiles in gold-catalysed reactions, there are a handful of seminal papers which demonstrate that it is indeed possible.

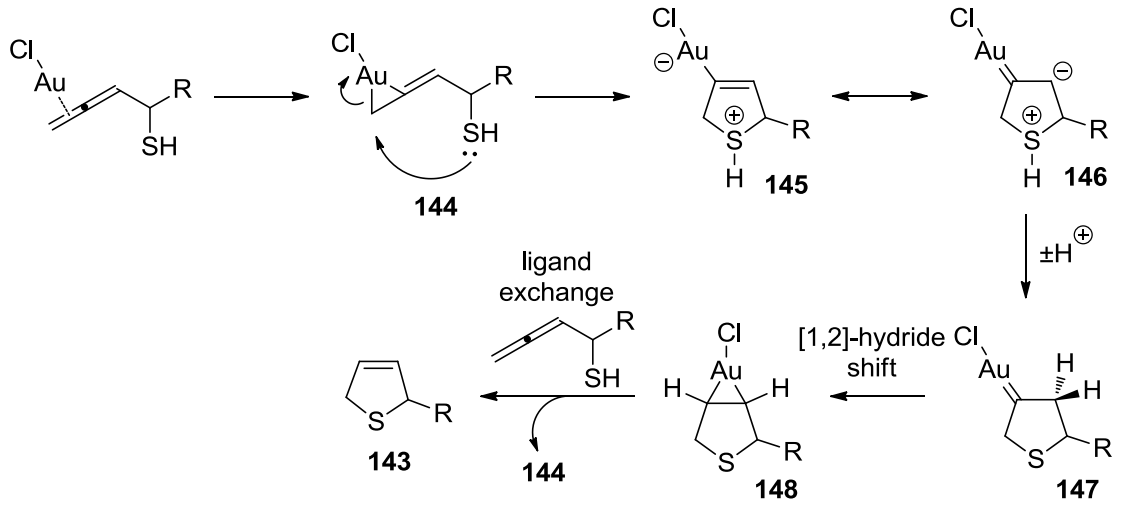
In 2006, Krause and co-workers revealed the first example of gold(I)-mediated carbon-sulfur bond formation.[15] This ground-breaking reaction was the intramolecular addition of thiols to allene functionalities, producing 2,5-dihydrothiophenes **143** (Scheme 3.1).



Scheme 3.1. Krause's intramolecular gold(I)-catalysed rearrangement of thioallenes.

The reaction was found to be tolerant of an additional alkene functionality within the starting material, however this did lead to a reduced yield of 43%. This was attributed to the possibility of the gold(I)-centre binding to this alkene functionality, thus diminishing the overall reactivity at the allene centre. It should also be noted that the use of Au(III) salts may also be utilised for this reaction, however in some cases a disulfide species was observed, presumably from the reductive elimination of Au(III) to Au(I).

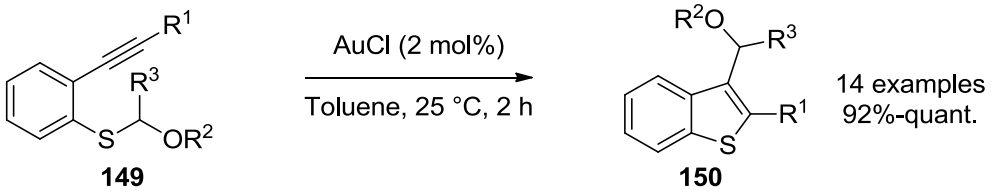
The authors discussed their proposed mechanism, in which the gold(I) catalyst activates the distant allenic double bond toward nucleophilic attack from the thiol. Protodemetallation then gives the desired 2,5-dihydrothiophene, with complete retention of chirality from the starting material. In 2010, Ando undertook a computational mechanistic study into this gold-catalysed rearrangement of thioallenes, the results showed some agreement with that put forward by Krause (Scheme 3.2).[16]



Scheme 3.2. Computationally calculated mechanism for the thioallene rearrangement by Ando.

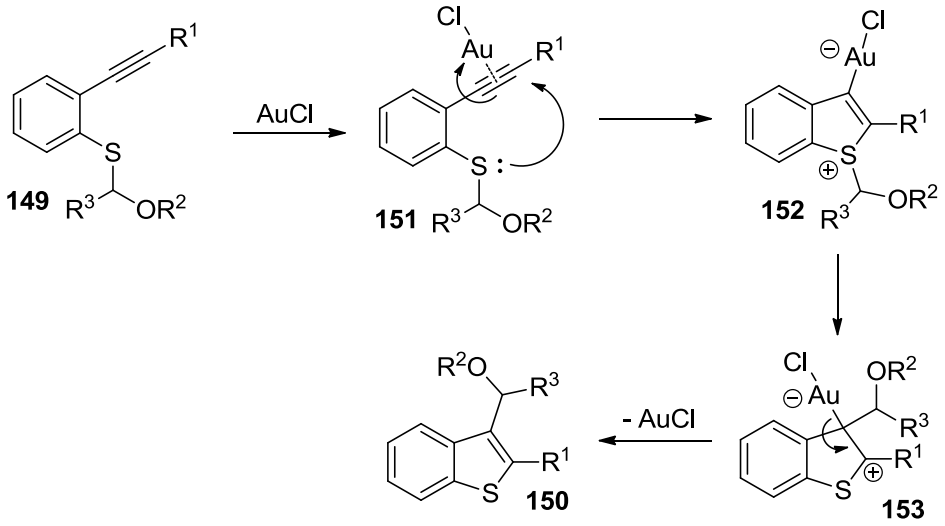
The calculations carried out by Ando suggest that the gold(I)-centre does indeed activate the allenic double bond furthest away from the sulfur moiety. Intramolecular sulfur attack can then occur, giving Zwitterionic species **145** and **146**. A proton transfer must then take place giving **147**; calculations suggest that this is the rate-determining step due to the high energy required to perform this transfer. However calculations which include the presence of a water molecule, as well as taking solvent interactions into account, severely reduced the predicted energy required to carry out this step. A [1,2]-hydride shift can then occur giving **148**, which releases the desired 2,5-dihydrothiophene **143** after ligand exchange with a molecule of starting material.

An intramolecular gold-catalysed cyclisation of (α-alkoxy alkyl)(*o*-alkynyl phenyl) sulfides **149** was reported by Nakamura and co-workers in 2006 (Scheme 3.3).[21] This high yielding, mild reaction was shown to be an efficient method of affording 2,3-disubstituted benzothiophenes **150**.



Scheme 3.3. Intramolecular cyclisation to access 2,3-disubstituted benzothiphenes, by Nakamura.

The formation of the product has been suggested to go *via* the pathway outlined in Scheme 3.4. The gold catalyst activates the alkyne triple bond toward nucleophilic attack by the sulfur (**151**), achieving cyclised intermediate **152**. A two-step migration of the (α-alkoxy alkyl) group to the gold-bearing carbon centre allows the formation of **153**. The desired product **150** is formed after elimination of the gold chloride catalyst.

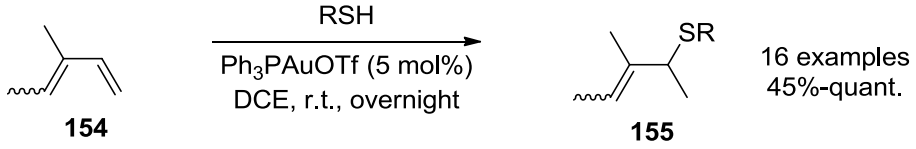


Scheme 3.4. Proposed mechanism of the gold-catalysed cyclisation by Nakamura.

3.1.2 Intermolecular Gold-Catalysed Reactions with Sulfur-Nucleophiles

The work detailed by Krause opened the door to a range of possible gold(I)-catalysed reactions with sulfur nucleophiles. It had been shown that reactions could remain high yielding, even when a known gold(I) poison was being used in the reaction, therefore work could then begin into achieving the more challenging *intermolecular* reactions.

The first to report a gold(I)-catalysed intermolecular thiol addition was He and co-workers in 2007.[17] A range of thiols were shown to react with conjugated olefins **154** to produce allylic thioethers **155** in impressive yields (Scheme 3.5).

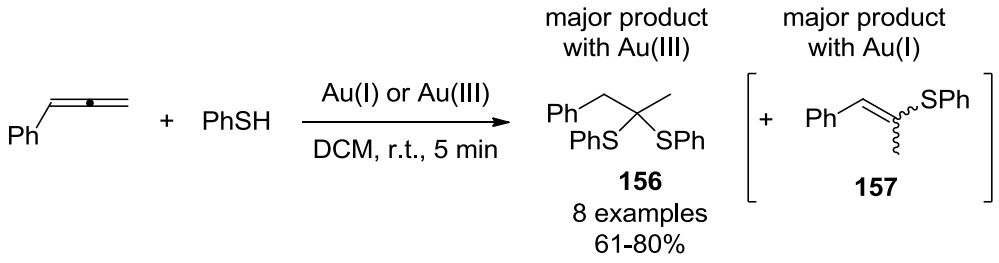


Scheme 3.5. Gold(I)-catalysed hydrothiolation of dienes by He.

A wide range of thiols were shown to be viable nucleophiles, including those with additional reactive functional groups (such as an alcohol group). With the reaction being carried out at room temperature, these mild conditions allow the use of labile groups on the thiol (such as a trimethylsilyl group). Previous methods of thiol addition to dienes used Brønsted acids or radical initiators, both potentially detrimental to labile or reactive groups on the thiol. Hence, He's mild gold(I)-catalysed method improved the overall scope of obtainable products.

There were certain limitations to this reaction, for example a thiol containing a primary amine group was found to undergo no reaction. Although the authors offer no explanation as to why this not a compatible group, it could be envisaged that the amine functionality strongly coordinates to the gold(I)-species, rendering it inactive in the catalytic cycle (see Chapter 4). Thiobenzoic acid was used as a potential nucleophile, however the desired product was not observed and instead polymerisation of the styrene substrate occurred. The use of a simple unactivated olefin was also investigated, but this offered no hydrothiolation product.

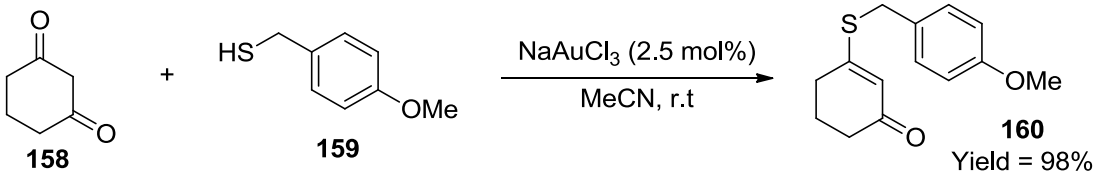
A gold-catalysed intermolecular hydrothiolation of allenes was reported by Yamamoto and co-workers in 2010 (Scheme 3.6).[18] The desired product of this reaction was the dithioacetal product **156**, which was formed in good yields with a range of substrates.



Scheme 3.6. Gold(I)-catalysed hydrothiolation of allenes by Yamamoto.

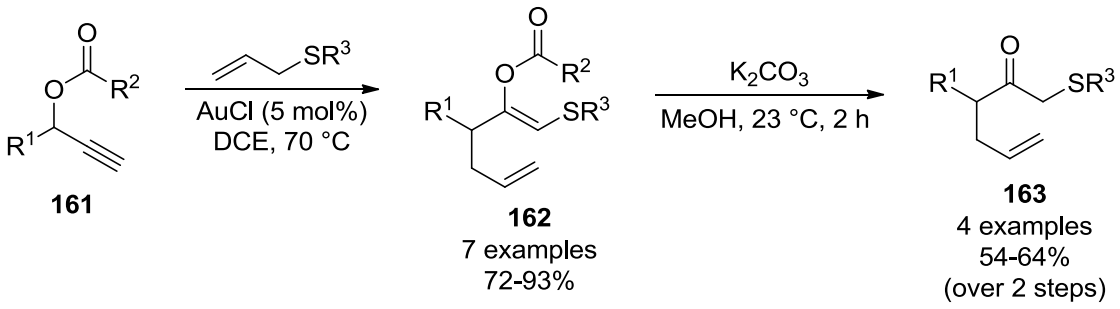
Although the optimised conditions utilised gold(III) as the catalyst, the initial catalyst screen indicated that gold(I) could also be used. However, a remarkable switch in selectivity is observed with gold(I). The dithioacetal no longer becomes the sole product, and instead vinyl sulfide **157** is obtained as the major product. Species **157** is suggested to be the intermediate toward desired product **156**, and the authors did not investigate this species any further for isolation or method development.

As part of an investigation carried out by Arcadi and co-workers in 2003, it was shown that gold(III) can catalyse the nucleophilic addition of a thiol **159** to 1,3-cyclohexanedione **158** (Scheme 3.7).[19] The primary aim of the report focussed on the addition of *N*-nucleophiles to 1,3-dicarbonyl species, however they were able to demonstrate that a sulfur-based nucleophile could also achieve an excellent yield of product **160**.



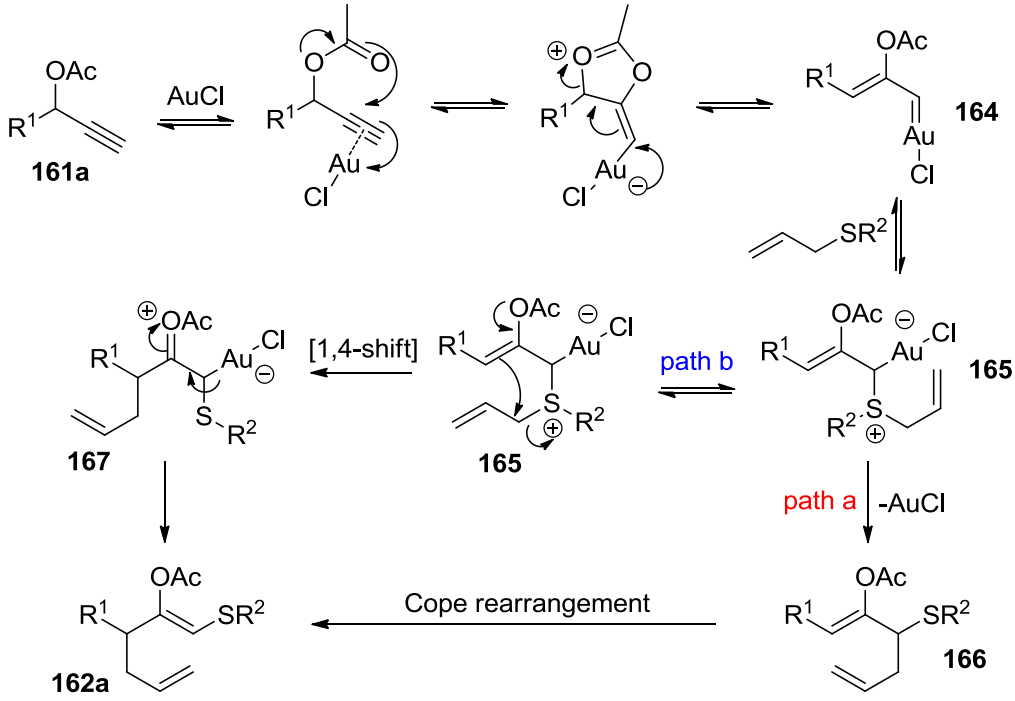
Scheme 3.7. Gold(III)-catalysed addition of a thiol to a 1,3-dicarbonyl species by Arcadi.

Another source of sulfur-based nucleophiles, which have found to be compatible with gold-catalysis, is sulfides. In 2008, Davies reported an intermolecular gold(I)-catalysed reaction of allyl sulfides with propargylic carboxylates **161** (Scheme 3.8).[34]



Scheme 3.8. Gold(I)-catalysed reaction of propargylic carboxylates and sulfides by Davies.

The reaction is high yielding, however when electron-deficient allyl sulfides are utilised, two equivalents of sulfide is required. Subsequently, the enol acetate products **162** of these electron-deficient substrates were hydrolysed to afford the corresponding ketones **163**. This made the purification process easier due to co-elution of the starting material sulfide.

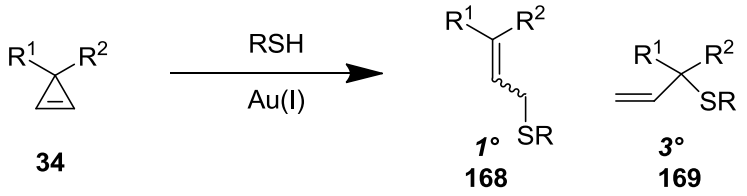


Scheme 3.9. Proposed mechanism of the gold-catalysed formation of enol acetates.

The proposed mechanism for the formation of the vinyl sulfide products **162** has two potential pathways (Scheme 3.9). The propargylic carboxylate **161** will undergo a rearrangement to give the gold-carbenoid species **164**. The allyl sulfide can then react to form the ylide **165**, at this point the mechanism can follow one of two pathways. The first (path a) involves a [2,3]-sigmatropic rearrangement, or a 1,2-shift of the allyl group to generate **166**. This then undergoes a Cope rearrangement to yield the desired product **162**. Alternatively, an oxygen-assisted 1,4-shift on intermediate **165** can take place to produce **167** (path b). The desired product **162** can be obtained after elimination of the gold chloride.

3.2 Project Aim

Having built up an understanding within the Lee Group of how cyclopropenes **34** react with various nucleophiles, the question on the feasibility of sulfur-based nucleophiles was raised. With sulfur being a known strong coordinator to gold centres, it was unknown whether this could be achievable. From previous work it is known that nucleophiles can add regioselectively to cyclopropenes to produce primary or tertiary substituted products, thiols could therefore potentially react to form **168** or **169** respectively (Scheme 3.10).



34 **168** **169**

Scheme 3.10. Possible reaction outcomes of gold(I)-catalysed thiol additions to cyclopropenes.

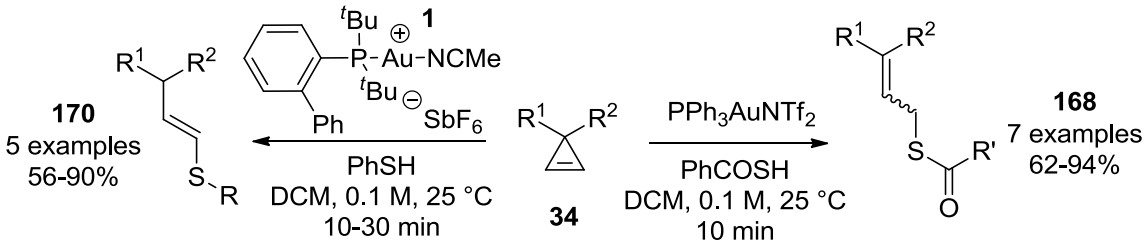
The aim of this project was to develop the gold(I)-catalysed nucleophilic addition of sulfur-based species to cyclopropenes. It would be advantageous to attempt to keep the reaction conditions as mild as possible, while limiting any need for additives.

The overall scope of the reaction was to be investigated, once the reaction was fully optimised. Studies into different types of sulfur nucleophiles was to be carried out, specifically looking at alkyl thiols, thiophenols and thioacids. Various thiols with potentially reactive groups were to be studied, to hopefully demonstrate the chemoselective nature of the reaction. A wide range of 3,3-disubstituted cyclopropenes were also to be explored, with the aim of determining whether the reaction is altered by steric bulk.

Finally, the mechanism of the reaction was to be probed. This was to be achieved by carrying out deuterium-labelling reaction. The insight gained in the mechanistic studies will hopefully shed light on how sulfur-based nucleophiles could be used more widely and successfully in gold-catalysis.

3.2.1 Previous Work within the Lee Group

The optimisation of this reaction was carried out by R. J. Mudd as part of his MChem project within the Lee Group. A range of reaction conditions were screened including: solvents, catalysts, temperature, concentration and stoichiometry. The optimised conditions are shown in Scheme 3.11, and it is important to note that the order of addition of reagents has an important effect on the outcome of the reaction. The gold(I) catalyst and the sulfur nucleophile must be premixed together in a small quantity of solvent before addition to the cyclopropene substrate **34**; this allows for smooth reaction through to the product. Mixing cyclopropene and thiol initially, before addition of the gold catalyst, results in desired products (e.g. **168**), contaminated with cyclopropane side-product **171**, produced from the uncatalysed background reaction (Figure 3.2).



Scheme 3.11. Optimised conditions for addition of sulfur-based nucleophiles to cyclopropenes.

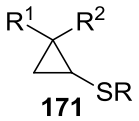


Figure 3.2. Uncatalysed cyclopropane side-product.

As shown in Scheme 3.11, there are different conditions for reactions with thiophenols, compared to the conditions required for thioacids. This will be discussed in further detail (*vide infra*). The products afforded from using thiophenols with **1** are vinyl thioethers **170**. Conversely, when thioacids are employed in the reaction with PPh_3AuNTf_2 the products are allylic thioesters **168**.

3.2.2 Further Project Aims

The work already carried out by R. J. Mudd in the Lee Group, had demonstrated that the selection of the gold catalyst was extremely important to the outcome to the reaction. To investigate this further, we planned to carry out a short catalyst and counterion screen to determine the selectivities of **168** and **170**. The results gained from this short investigation will hopefully shed light on which gold(I) catalysts are more tolerant to sulfur nucleophiles in reactions.

So far, thiophenols and thioacids had been investigated as nucleophiles (Scheme 3.11), so we were keen to investigate the more nucleophilic alkyl thiols. With the optimised conditions in hand, it would also be beneficial to study the functional group compatibility of the reaction. To do this, a nucleophile screen was to be carried out using thiols with additional functional groups. This should confirm if the reaction is chemoselective, *i.e.* reacts solely at the *S*-position, rather than any other potentially nucleophilic group.

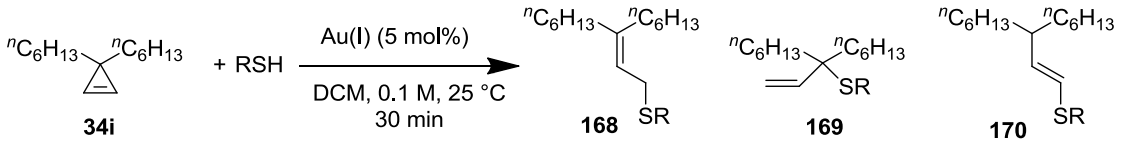
To assist in the determination of how the reaction proceeds, some mechanistic studies need to be carried out. This should help shed light into the different species formed in the reaction, and will in turn aid the overall understanding on how gold(I)-catalysis with sulfur nucleophiles can be developed in the future.

3.3 Results & Discussion

3.3.1 Reaction Optimisation & Scope

As part of our optimisation studies a short catalyst screen was performed, in order to investigate how ligand and counterion affects the selectivity of the reaction. The results showed a great variation in product ratios and the appearance of side-product **171** (Table 3.1).

Table 3.1 Gold(I) catalyst and counterion screen for thiol & thioacid additions to cyclopropenes.



34i **168** **169** **170**

Entry	RSH	Catalyst	Isolated Yield	Products	Ratio 168:169:170[a]
1	MeCOSH	PPh_3AuNTf_2	76%	**168a:169a**	9:1:0
2	MeCOSH	**1**	85%	**168a:170a**	2:0:1
3	MeCOSH	(IPr)AuCl / $AgSbF_6$	71%	**168a:169a:170a**	9:1.2:1
4	MeCOSH	(IPr)AuCl / AgOTf	N/D [b]	**168a:170a**	99:0:1
5	MeCOSH	PPh_3AuCl / $AgSbF_6$	77%	**168a:169a:170a**	58:5:1
6	PhSH	PPh_3AuNTf_2	0 [c]	-	-
7	PhSH	**1**	72%	**170b** [d]	All **170b**
8	PhSH	(IPr)AuCl / $AgSbF_6$	89% [e]	**170b**	All **170b**
9	PhSH	PPh_3AuCl / $AgSbF_6$	75% [e]	**170b**	All **170b**
10	PhSH	PPh_3AuCl / AgOTs	0 [c]	-	-

[a] Determined by ^{1}H NMR analysis. [b] Unidentified inseparable side product. [c] Only unreacted starting material observed. [d] 16:1 *E*:*Z*. [e] Cyclopropane **171a** 60% of reported yield.

Varying the catalyst when using thioacetic acid showed that the NHC-catalyst, (IPr)$AuSbF_6$, and PPh_3AuSbF_6 (both formed *in situ*) performed similarly in yield to the commercially available PPh_3AuNTf_2 catalyst (entries 3 & 5 *vs*. entry 1). However, with these two *in situ* formed catalysts small quantities of product **170a** was observed. Changing the counterion to a more coordinating OTf group altered the product ratio by producing **168a** as the major isomer, albeit with an unidentified inseparable side product (entry 4). Using catalyst **1** gave an improved yield compared to PPh_3AuNTf_2 (entry 2 *vs.* entry 1), disappointingly the selectivity is severely reduced to 2:1 **168a**:**170a**. This considerable reduction in selectivity dictated that PPh_3AuNTf_2 would be the catalyst used in the reaction with thioacids.

If thiophenol is used with catalyst PPh_3AuNTf_2, no reaction occurs and only unreacted starting material is observed (entry 6). The probable explanation for this is that the gold(I) catalyst has been deactivated by the thiophenol to such an extent that it is no longer catalytically active. Switching the catalyst to the cationic species **1**, the reaction proceeds with high yield and results in only one isomer being formed **170b** (entry 7). This can be attributed to catalyst **1** being more tolerant toward deactivation by thiophenol, compared to PPh_3AuNTf_2.

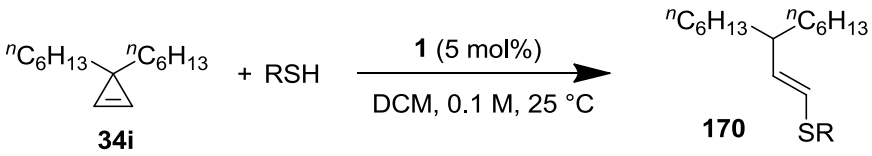
Similar highly regioselective gold(I)-catalysed reactions occur with both (IPr)$AuSbF_6$ and PPh_3AuSbF_6 (entries 8 & 9), however the uncatalysed cyclopropane side product **171a** was observed in high quantities (60%). Altering the counter ion to much more coordinating OTs group proved severely detrimental to the reaction, with only unreacted starting material observed (entry 10).

From this short catalyst and counterion screen, it can be concluded that the counterion attached to the gold catalyst is in fact the most influential characteristic, rather than the ligand. The more coordinating counterions (such as NTf_2 and OTs) are more susceptible to deactivation, compared to the weakly bound SbF_6 counterion. Hence, for reactions involving the less nucleophilic thioacids, PPh_3AuNTf_2 was selected as the catalyst to be used to form **168a** selectively. When thiophenols and alkyl thiols were used, the more tolerant **1** was selected to regioselectively form **170**.

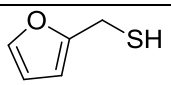
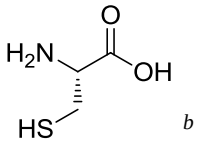
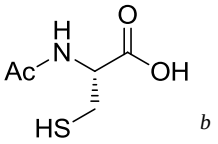
The main substrate scope of this reaction (using thiophenols and thioacids) was carried out by R. J. Mudd (MChem project student), and was reported in the published article.[35]

To expand on these results, we investigated alkyl thiols as well as several thiols bearing potentially reactive groups to determine whether this reaction could be deemed chemoselective (Table 3.2). All results were highly regioselective, yielding one product **170**, with **168** and **169** not observed in any ^{1}H NMR spectra of crude reaction mixtures.

Table 3.2 Screen of thiol nucleophiles.



34i **170**

Entry	RSH	Time (min)	Isolated Yield	*E*:*Z* Ratio [a]
1	^{n}BuSH	360	48% **170c**	>20:1
2	^{t}BuSH	1200	84% **170d**	>20:1
3		60	86% **170e**	>20:1
4	$HO(CH_2)_2SH$	180	82% **170f**	>20:1
5	$HO_2C(CH_2)_2SH$	120	73% **170g**	>20:1
6	 [b]	60	-	-
7	 [b]	60	-	-

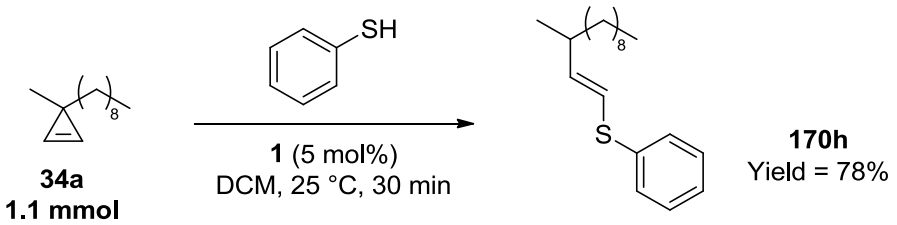
[a] Determined by ^{1}H NMR analysis. [b] Insoluble in DCM.

Firstly, it was observed that alkyl thiol nucleophiles (Table 3.2) require a much longer reaction time (60-1200 min) compared to thiophenols (30 min) or thioacids (10 min). Switching from *n*-butylthiol to *t*-butylthiol was beneficial to the yield of the reaction, going from 48% to 84% (entries 1 & 2), although using *t*-butylthiol also required a much longer reaction time. This is presumably due to it being more Lewis basic compared to the *n*-butylthiol, and therefore has a greater ability to deactivate the gold(I) catalyst. Alternatively, the product from *n*-butylthiol may be more volatile, and this could account for the reduction in yield.

Adding potentially reactive functionalities to the thiols was then investigated. Furfuryl mercaptan was shown to chemoselectively react at the thiol position achieving a very good 86% yield (entry 3), even though previously it has been shown that furans will react extremely well with cyclopropenes, in the presence of gold(I) catalysts.[36] 2-Mercaptoethanol was similarly shown to react in a chemoselective manner at the *S*-position of the nucleophile, affording a good 82% isolated yield (entry 3). Alcohols have also been reported to react with cyclopropenes, however no evidence of this occurring was observed in this reaction.[37-39] In addition to these two examples, 3-mercaptopropionic acid was shown to react only at the thiol end of the molecule, leaving the acid group free for further potential functionalisation.

Unfortunately, L-cysteine and *N*-acetyl-L-cysteine (entries 6 & 7) were found to be insoluble in DCM. Therefore, no reaction took place with the cyclopropene. This would have been highly desirable as a method of functionalising thiol-bearing amino acids. Further development of this reaction could include reoptimising the reaction conditions to include these potential nucleophiles being tolerated.

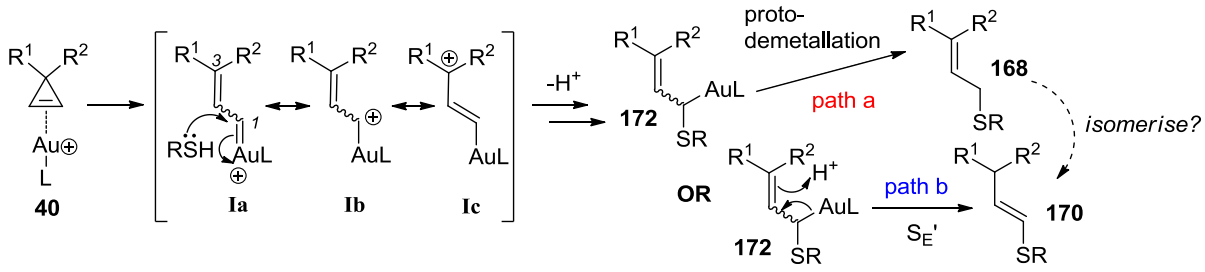
Next, in order to demonstrate the usefulness of this reaction, a larger scale experiment was attempted (Scheme 3.12). The reaction was carried out on 1.11 mmol scale (equivalent to 200 mg of cyclopropene **34a**), and a very respectable yield of 78% was achieved (compared to 84% at 0.061 mmol).



Scheme 3.12. Larger scale reaction of gold(I)-catalysed thiol addition to cyclopropene.

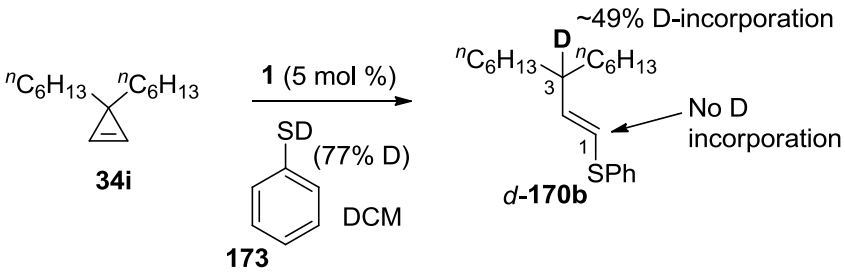
3.3.2 Mechanistic Studies

The proposed mechanism is outlined in Scheme 3.13. Gold(I) activates the cyclopropene alkene bond, which undergoes ring opening.[38, 40] The ring-opened intermediate can be drawn in three resonance forms **Ia-c**, nucleophilic attack by sulfur can then occur at the C1 position on this intermediate. Protodemetallation of this new intermediate **172** will afford the allylic thioesters **168** (path a). Alternatively, the intermediate **172** can undergo an S_E' mechanism to yield the vinyl thioether **170** (path b). It can also be envisaged that the vinyl thioether **170** could be a product of isomerisation from the allylic species **168**.



Scheme 3.13. Possible pathways to obtain **168** and **170**.

A deuterium-labelling study was performed, with the prospect of uncovering which pathway operates to obtain product **170** (Scheme 3.14). Thiophenol was labelled with deuterium[41] to be used in the gold(I)-catalysed reaction with cyclopropene **34i**. The product only showed deuterium-incorporation at the C3 position, thus suggesting that path b of Scheme 3.13 is correct. The evidence for this pathway is strengthened by the fact that no isomerisation to product **170b** takes place when species **168b** is resubjected to the reaction conditions.



Scheme 3.14. Deuterium labelling studies.

It has already been verified that certain gold(I) catalysts are more tolerant toward deactivation by sulfur nucleophiles, compared to others (*vide supra*, Table 3.1). The cationic catalyst **1** was shown to tolerate alkyl thiols and thiophenols in the reaction, whereas PPh_3AuNTf_2 (with a more coordinating counterion) was shown to be inactive with these nucleophiles and only tolerated reactions with thioacids.

As part of the mechanistic studies for this reaction, the true nature of this deactivation was studied. Therefore an NMR study was carried out, looking at changes in both the ^{1}H and ^{31}P NMR spectra of the catalyst after addition of thiophenol.

To replicate the reaction conditions, a 20:1 mixture of thiophenol:**1** was dissolved in deuterated DCM. ^{1}H and ^{31}P NMR spectra were obtained, and compared against the original spectra of catalyst **1**. It was clearly evident that the structure of the catalyst had significantly changed. The chemical shift of the loosely-bound MeCN ligand had moved from 2.39 ppm to 1.97 ppm on the addition of thiophenol (Figure 3.3). Likewise, the ^{31}P chemical shift of the phosphorus ligand attached to the gold had shifted from 57.3 ppm in the parent catalyst, to 62.9 ppm (Figure 3.4).

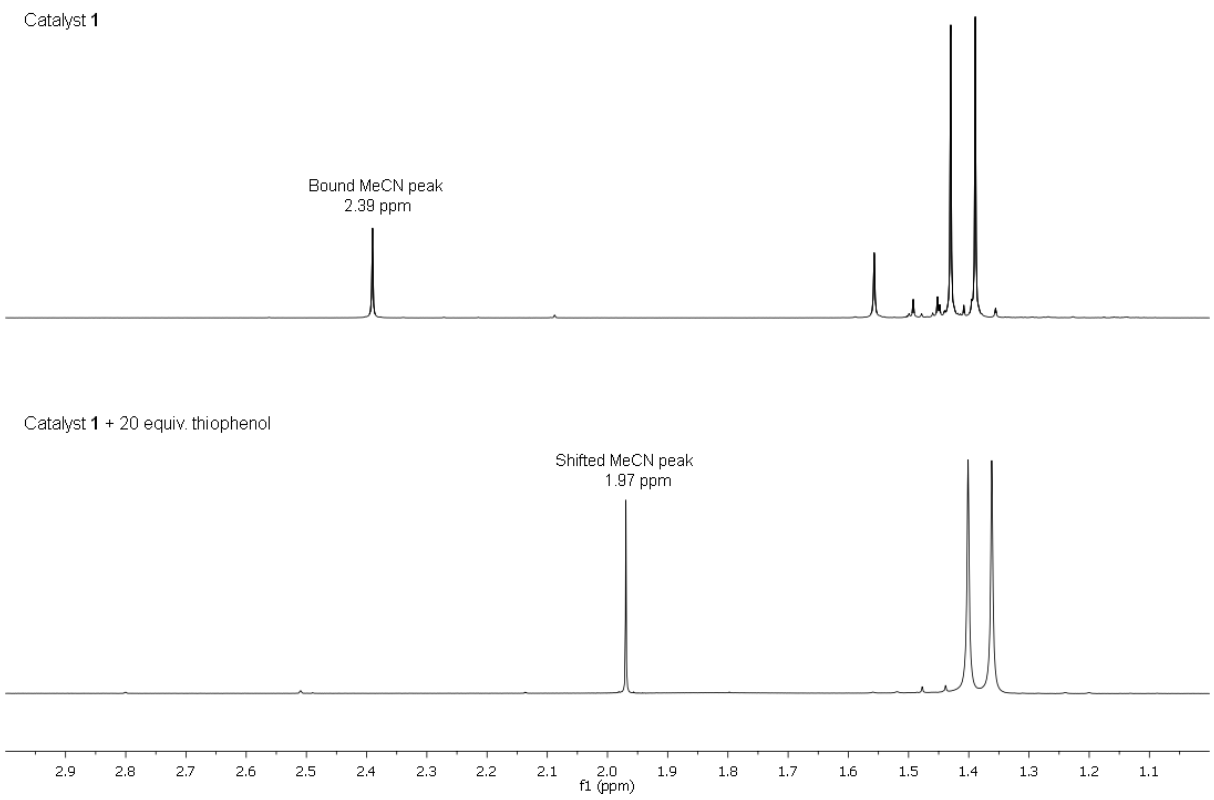


Figure 3.3. Shift in MeCN peak in ^{1}H NMR before and after addition of thiophenol.

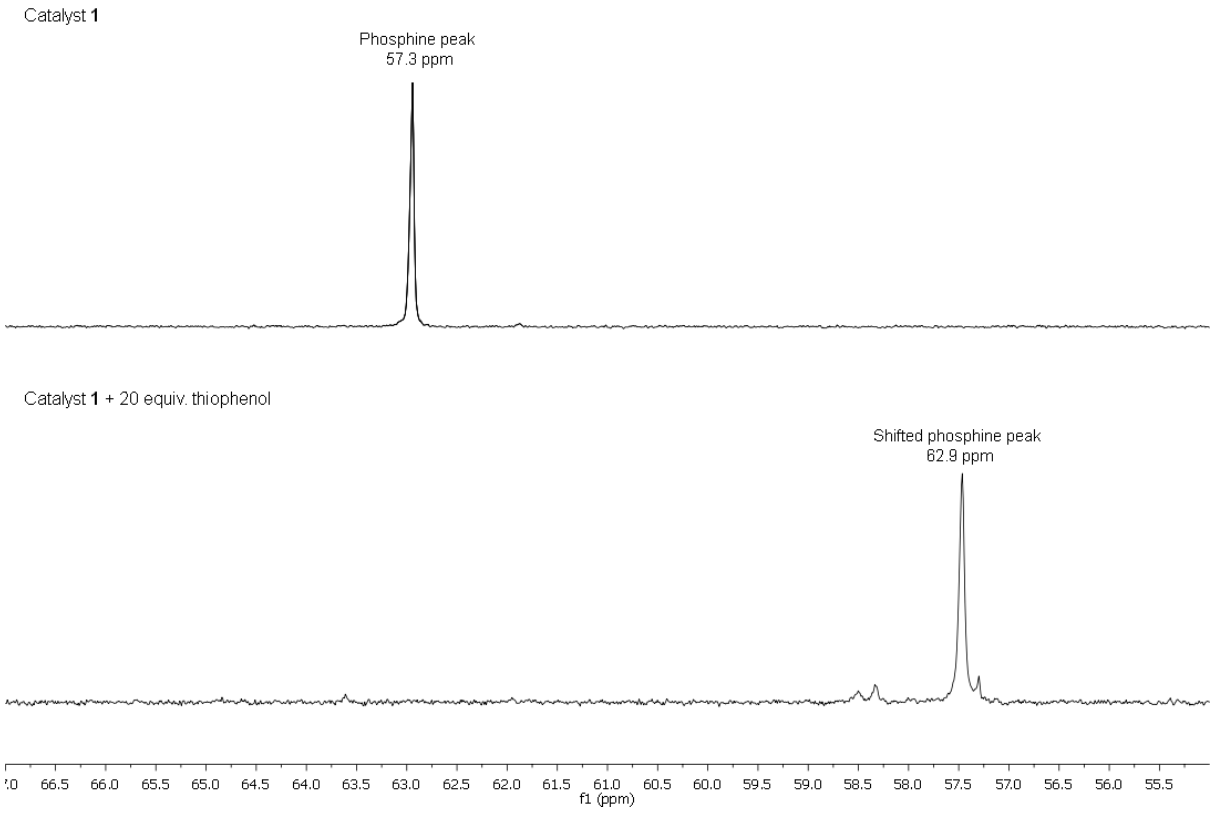


Figure 3.4. Shift in phosphine ligand peak in ^{31}P NMR before and after addition of thiophenol.

This exact trend was observed when a 1:1 mixture of thiophenol:**1** was prepared in deuterated DCM. From this solution, crystals were obtained *via* slow evaporation of the NMR sample. X-ray crystallography confirmed that complex **174a** had been formed (Figure 3.5); a novel digold structure with bridging thiolate.

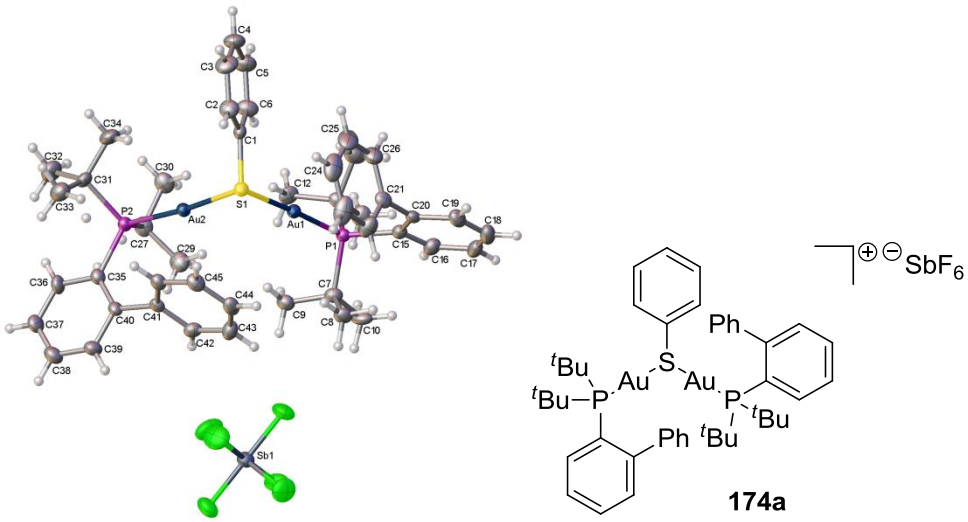
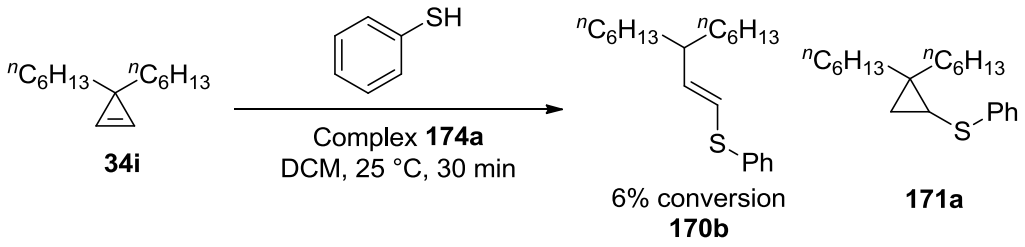


Figure 3.5. Novel digold species with bridging thiolate.

This complex was then subjected to the reaction conditions as a catalyst with thiophenol and cyclopropene **34i** (Scheme 3.15). A very poor conversion of 6% to product **170b** was observed, suggesting that this is not a highly catalytically active species. The major product from this reaction was found to the uncatalysed cyclopropane product **171a**. A control reaction shows that with the absence of gold(I) catalyst, only cyclopropane **171a** is attained. Since there is evidence of product **170b** being formed in minimal quantities, it suggests that there is some form of catalytic activity, however it is highly inefficient.



Scheme 3.15. Reaction using complex **174a** as the catalyst.

Structures similar to complex **174a** could account for the diminished catalytic activity observed in some gold(I)-catalysed reactions with sulfur nucleophiles. If these types of species form, catalytic conversion of starting materials to products cannot proceed. However, if the formation of these structures were actually in equilibrium with the catalytically active parent catalyst, the reaction may be able to advance. The formation of digold with bridging thiolate species, such as **174a**, and their catalytic activity will be discussed in further detail throughout Chapter 4.

3.4 Conclusions & Future Work

A gold(I)-catalysed addition of thiols and thioacids to 3,3-disubsituted cyclopropenes **34** was developed. The reaction with alkyl thiols and thiophenols to obtain vinyl thioethers **170** require the use of the cationic gold catalyst **1**, as it is more tolerant toward deactivation by the sulfur nucleophile. However, the reaction involving the less nucleophilic thioacid, to produce allylic thioesters **168** regioselectively utilises PPh_3AuNTf_2 as the catalyst.

The reactions were demonstrated to be very mild and high yielding. Thiols with potentially reactive groups were shown to react *chemoselectively* at the *S*-position, even in cases where the additional group has previously been shown to react with cyclopropenes (*e.g.* furan and alcohol).

The nature of the deactivated gold(I) species was identified as being a digold species with bridging thiolate (e.g. **174a**). The isolated complex was found to be highly inefficient at catalysing the desired reaction, however may shed some light into the types of species formed in gold(I) catalysis with sulfur nucleophiles. The formation of these species is the subject of Chapter 4.

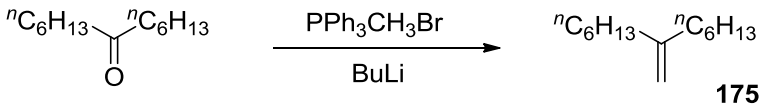
3.5 Experimental

General Experimental Section

^{1}H NMR spectra were recorded on Bruker AV 300 and AV 400 spectrometers at 300 and 400 MHz respectively and referenced to residual solvent. ^{13}C NMR spectra were recorded using the same spectrometers at 75 and 100 MHz respectively. Chemical shifts (δ in ppm) were referenced to tetramethylsilane (TMS) or to residual solvent peaks ($CDCl_3$ at δ_H 7.26). *J* values are given in Hz and s, d, dd, t, q, qn and m abbreviations correspond to singlet, doublet, doublet of doublet, triplet, quartet, quintet and multiplet. Mass spectra were obtained at the EPSRC National Mass Spectrometry Service Centre in Swansea. Infrared spectra were obtained on Perkin-Elmer Spectrum 100 FT-IR Universal ATR Sampling Accessory, deposited neat or as a chloroform solution to a diamond/ZnSe plate. Flash column chromatography was carried out using Matrix silica gel 60 from Fisher Chemicals and TLC was performed using Merck silica gel 60 F254 precoated sheets and visualised by UV (254 nm) or stained by the use of aqueous acidic $KMnO_4$ or aqueous acidic ceric ammonium molybdate as appropriate. Petrol ether refers to petroleum ether (40–60 °C). Tetrahydrofuran was dried by distillation from sodium – benzophenone under nitrogen. Dichloromethane (DCM) was purchased from Fisher and used without further purification. All thiol substrates were purchased and used without further purification. The silver salts used were stored and weighed out in a glove box. The gold(I)-catalysed reactions were carried out without the need for dry solvents or inert atmosphere, except for the deuterium labelling study.

Cyclopropene starting materials:

7-Methylenetridecane **175**:[42]

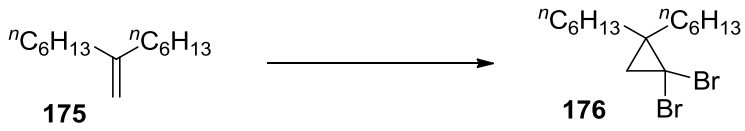


175

To a stirred solution of Ph_3PCH_3Br (17.45 g, 48.8 mmol) in THF (70 mL) at 0 °C was added 1.6 M *n*-butyllitium (28.5 mL, 45.6 mmol) dropwise over 60 minutes. The reaction mixture was stirred for 1 hour at room temperature. Dihexyl ketone (5.00 g, 25.2 mmol) in THF (10 mL) was added dropwise to the reaction mixture over 5 hours. The reaction was then stirred at room temperature overnight, quenched with saturated NH_4Cl (50 mL), diluted with water (30 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with brine (70 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The product was isolated by flash column chromatography (eluent: *n*-pentane) to yield **175** as a colourless oil (2.79 g, 14.2 mmol, 57%).

ν_{max}/cm^{-1} 2957 m 2926 s 2857 s (C-H), 1645 m (C=C), 1466 m (alkyl C-H bend), 887 s (alkene C-H bend); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.69 (s, 2H, C=C$\underline{H}_2$), 2.09 – 1.90 (t, *J* = 7.6 Hz, 4H, 2 × CH_2=CC$\underline{H}_2$), 1.51 – 1.18 (m, 16H, alkyl CH_2), 0.89 (t, *J* = 6.7 Hz, 6H, 2 × $CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6 (C), 108.5 (CH_2), 36.3 (CH_2), 32.0 (CH_2), 29.3 (CH_2), 28.0 (CH_2), 22.8 (CH_2), 14.3 (CH_3).

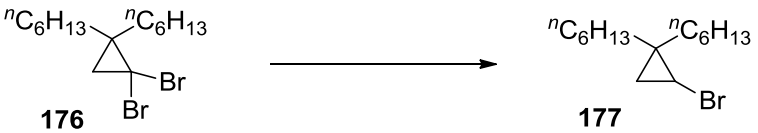
1,1-Dibromo-2,2-dihexylcyclopropane **176**:



Bromoform (2.4 mL, 26.5 mmol) and DCM (0.6 mL) were added dropwise over 30 minutes to a stirring mixture of aqueous sodium hydroxide (5.8 mL, 10 M), alkyltrimethylammonium bromide (0.54 g), 7-methylenetridecane **175** (2.59 g, 13.2 mmol) and DCM (2.5 mL). The mixture was allowed to stir vigorously at 35 ^{o}C overnight. The reaction mixture was then diluted with water (30 mL). DCM (40 mL) was added and layers partitioned. The aqueous layer was washed twice with DCM (40 mL). The combined organic layers were washed with brine (60 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting material was purified by flash column chromatography (hexane) and the remaining bromoform was evaporated under high vacuum (21 h, 35 ^{o}C) to yield titled compound **176** (4.33 g, 11.7 mmol, 89%) as a colourless oil.

ν_{max}/cm^{-1} 2954 m 2925 s 2857 m (C-H), 1457 m (alkyl C-H bend); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73 – 1.19 (m, 22H, alkyl C$\underline{H}_2$ & C$\underline{H}_2$CBr$_2$), 0.95 – 0.83 (m, 6H, 2 × CH$_2$C$\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.3 (C), 35.1 (CH_2), 34.4 (CH_2), 33.3 (C), 31.9 (CH_2), 29.5 (CH_2), 26.3 (CH_2), 22.8 (CH_2), 14.2 (CH_3); Found (APCI) $[M+H]^+$ 367.0627, $C_{15}H_{29}Br_2$ requires 367.0631.

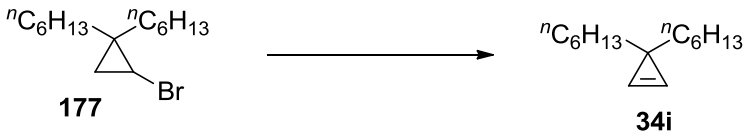
2-Bromo-1,1-dihexylcyclopropane **177**:



A solution of ethylmagnesium bromide (1.0 M in THF, 13 mL, 13 mmol) was added over 1.5 hours to a stirring solution of **176** (4.00 g, 10.9 mmol), Ti(O^iPr)$_4$ (0.33 mL, 1.09 mmol) and THF (35 mL). The solution was allowed to stir for an additional 3 hours at room temperature. The reaction was quenched by slow addition of water (35 mL), then 20% aqueous sulfuric acid (80 mL) was added and the resulting mixture was stirred for 30 minutes. Diethyl ether (70 mL) was added and the layers were partitioned. The aqueous layer was washed a further two times with diethyl ether (70 mL). The combined organic layers were washed with saturated sodium bicarbonate (90 mL), washed with brine (90 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (pentane) to yield the titled compound **177** (2.34 g, 8.09 mmol, 74%) as a colourless oil.

ν_{max}/cm^{-1} 2956 m 2925 s 2857 m (C-H), 1458 m (alkyl C-H bend); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.82 (dd, *J* = 7.6, 4.3 Hz, 1H, C<u>H</u>Br), 1.58 – 1.14 (m, 20H, alkyl CH_2), 0.97 – 0.81 (m, 7H, 2 × C<u>H$_3$</u> & CHBrC<u>H</u>H'), 0.60 (dd, *J* = 6.0, 4.3 Hz, 1H, CHBrCH<u>H'</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.5 (CH_2), 33.3 (CH_2), 32.0 (CH_2), 32.0 (CH_2), 30.3 (CH), 29.7 (CH_2), 29.6 (CH_2), 26.3 (CH_2), 26.1 (CH_2), 25.0 (C), 22.8 (CH_2), 22.8 (CH_2), 22.2 (CH_2), 14.3 (CH_3), 14.2 (CH_3); Found (APCI) $[M+H]^+$ 289.1518, $C_{15}H_{30}Br$ requires 289.1525.

3,3-Dihexylcycloprop-1-ene **34i**:[43]

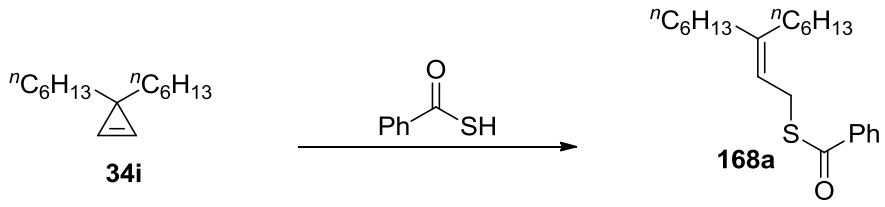


177 **34i**

Potassium *tert*-butoxide (1.44 g, 12.8 mmol) was dissolved in DMSO (20 mL). **177** (2.30 g, 7.95 mmol) was added dropwise over 15 minutes. The reaction mixture was allowed to stir overnight at 55 °C, and then quenched by addition of water (100 mL). Pentane (100 mL) was added and the layers partitioned. The aqueous layer was washed four times with pentane (50 mL). The combined organic layers were washed three times with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting material was purified by flash column chromatography (pentane) to titled compound **34i** (1.37 g, 6.57 mmol, 88%) as a colourless oil.

ν_{max}/cm^{-1} 2958 m 2921 s 2853 m (C-H), 1629 w (C=C) 1457 m (alkyl C-H bend); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (s, 2H, C<u>H</u>=C<u>H</u>), 1.47 – 0.97 (m, 20H, alkyl C<u>H$_2$</u>), 0.87 (t, *J* = 6.9 Hz, 6H, 2 × C<u>H$_3$</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 120.1 (CH), 38.8 (CH_2), 32.2 (CH_2), 29.6 (CH_2), 27.2 (CH_2), 24.8 (C), 22.9 (CH_2), 14.3 (CH_3); Found (APCI) $[M+H]^+$ 209.2258, $C_{15}H_{29}$ requires 209.2264.

S-3-Hexylnon-2-enyl benzothioate **168a**:

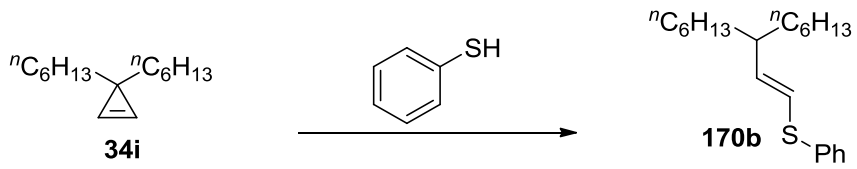


A solution of thiobenzoic acid (7.5 μL, 8.7 mg, 0.064 mmol) and PPh_3AuNTf_2 (2:1 toluene complex, 2.3 mg, 0.0031 mmol) in DCM (0.31 mL), was added to a solution of 3,3-dihexylcycloprop-1-ene **34i** (13 mg, 0.062 mmol) in DCM (0.31 mL) at 25 ^oC and stirred for 10 min. The solution was then concentrated under reduced pressure and filtered through a plug of silica (hexane:Et_2O, 10:1). The crude mixture was then purified using flash column chromatography (hexane:Et_2O, 50:1) to yield a 9:1 ratio of **168a**:**169a** (17.2 mg, 0.0496 mmol, 80%) as a clear colorless oil.

ν_{max}/cm^{-1} 2955 w (C-H), 2925 m (C-H), 2855 w (C-H), 1662 s (C=O); 1597 w, 1581 w, 1448 m (Ar C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 – 7.40 (m, 5H, Ar-H), 5.31 (t, *J* = 7.7 Hz, 1H, C=C<u>H</u>), 3.78 (d, *J* = 7.7 Hz, 2H, CHC<u>H_2</u>), 2.14 (t, *J* = 7.4 Hz, 2H, CC<u>H_2</u>), 2.04 (t, *J* = 7.4 H, 2H, CC<u>H_2</u>), 1.50 – 1.23 (m, 16H, alkyl CH_2), 0.99 – 0.82 (m, 6H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.3 (C), 145.4 (C), 137.2 (C), 133.2 (CH_2), 128.6 (CH), 127.2 (CH), 118.0 (CH), 36.9 (CH_2), 31.8 (CH_2), 31.8 (CH_2), 30.3 (CH_2), 29.7 (CH_2), 29.1 (CH_2), 28.6 (CH_2), 27.9 (CH_2), 27.2 (CH_2), 22.6 (CH_2), 22.6 (CH_2), 14.1 (2 × CH_3); Found (ESI) $[M+H]^+$ 347.2403, $C_{22}H_{35}OS$ requires 347.2406.

Representative procedure for gold-catalyzed thiophenol or thiol additions to 3,3-disubstituted cyclopropenes to form vinyl thioether:

(*E*)-(3-Hexylnon-1-enyl)(phenyl)sulfane **170b**:

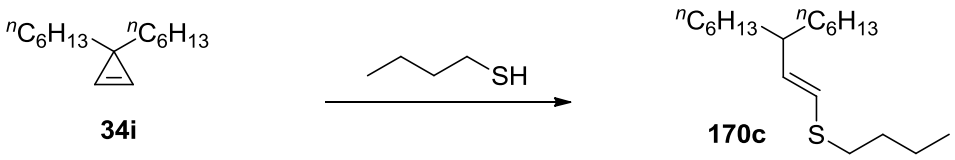


34i **170b**

A solution of thiophenol (7 μL, 8.1 mg, 0.065 mmol) and catalyst **1** (2.5 mg, 0.003 mmol) in DCM (0.33 mL), was added to a solution of 3,3-dihexylcycloprop-1-ene **34i** (13.6 mg, 0.065 mmol) in DCM (0.32 mL) at 25 ^{o}C and stirred for 30 min. The solution was then concentrated under reduced pressure and filtered through a plug of silica (hexane:Et_2O, 10:1). The crude mixture was then purified using flash column chromatography (hexane:Et_2O, 50:1) to yield (*E*)-(3-hexylnon-1-enyl)(phenyl)sulfane **170b** (15 mg, 0.047 mmol, 72%) as a clear colorless oil.

ν_{max}/cm^{-1} 2955 m (C-H), 2923 s (C-H), 2853 m (C-H), 1584 w, 1479 m, 1466 m (Ar C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.12 (m, 5H, Ar-H), 6.10 (d, *J* = 14.9 Hz, 1H, CH=C<u>H</u>S), 5.79 (dd, *J* = 9.2, 14.9 Hz, 1H, CHC<u>H</u>=CHS), 2.20 – 2.07 (m, 1H, C<u>H</u>CH=CHS), 1.51 – 1.19 (m, 20H, alkyl CH_2), 1.00 – 0.83 (m, 6H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1 (CH), 137.0 (C), 129.9 (CH), 128.1 (CH), 125.9 (CH), 119.9 (CH), 43.8 (CH), 35.1 (CH_2), 31.9 (CH_2), 29.4 (CH_2), 27.3 (CH_2), 22.7 (CH_2), 14.2 (CH_3); Found (APCI) $[M+H]^+$ 319.2455, $C_{21}H_{35}S$ requires 319.2454.

(*E*)-Butyl(3-hexylnon-1-en-1-yl)sulfane **170c**:

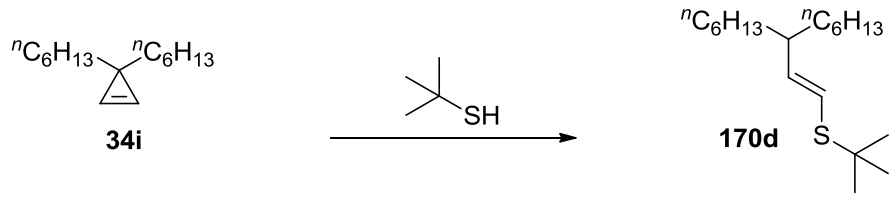


34i **170c**

Cyclopropene **34i** (15.2 mg, 0.073 mmol) was dissolved in DCM (0.30 mL). Catalyst **1** (2.8 mg, 0.0036 mmol) was added to a separate vial and dissolved in DCM (0.42 mL). n-Butyl mercaptan (7.7 µL, 6.5 mg, 0.072 mmol) was added to the vial using a Hamilton syringe. The mixture from the vial was then immediately transferred to cyclopropene **34i** *via* syringe. The reaction was allowed to stir at 25 °C for 6 hours, then the crude mixture was filtered through a short plug of silica using 10:1 hexane:diethyl ether. The desired product was purified using flash column chromatography (pentane → hexane → 50:1 hexane:diethyl ether), to yield **170c** as a colourless oil as a mixture of *E*:*Z* isomers in >20:1 ratio (10.5 mg, 0.035 mmol, 48%).

ν_{max}/cm^{-1} 2956 m 2925 s 2854 m (C-H), 1602 w (C=C), 1457 m (alkyl C-H bend); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82 (d, *J* = 7.2 Hz, 1H, CH=C<u>H</u>S), 5.36 (dd, *J* = 15.0, 9.1 Hz, 1H, C<u>H</u>=CHS), 2.63 (t, *J* = 7.3 Hz, 2H, SC<u>H$_2$</u>CH$_2$), 2.03 – 1.91 (m, 1H, SCH=CHC<u>H</u>), 1.66 – 1.12 (m, 24H, alkyl CH_2), 0.95 – 0.84 (m, 9H, 3 × CH_2C<u>H$_3$</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.3 (CH), 122.1 (CH), 43.9 (CH), 35.5 (CH_2), 32.7 (CH_2), 32.0 (CH_2), 31.8 (CH_2), 29.6 (CH_2), 27.4 (CH_2), 22.8 (CH_2), 22.0 (CH_2), 14.3 (CH_3), 13.9 (CH_3). Found (APCI) $[M+H]^+$ 299.2769, $C_{19}H_{39}S$ requires 299.2767.

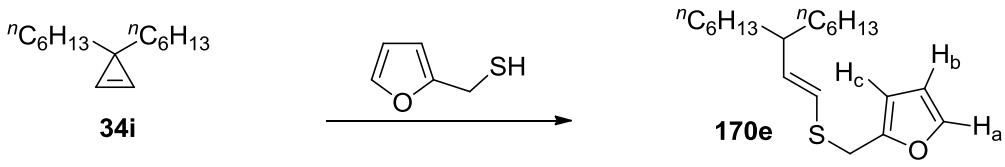
(*E*)-*tert*-Butyl(3-hexylnon-1-en-1-yl)sulfane **170d**:



Cyclopropene **34i** (15.0 mg, 0.072 mmol) was dissolved in DCM (0.30 mL). Catalyst **1** (2.8 mg, 0.0036 mmol) was added to a separate vial and dissolved in DCM (0.42 mL). *t*-Butyl mercaptan (8.1 µL, 6.5 mg, 0.072 mmol) was added to the vial using a Hamilton syringe. The mixture from the vial was then immediately transferred to cyclopropene **34i** *via* syringe. The reaction was allowed to stir at 25 °C for 22 hours, then the crude mixture was filtered through a short plug of silica using 10:1 hexane:diethyl ether. The desired product was purified using flash column chromatography (hexane → 50:1 hexane:diethyl ether), to yield **170d** as a colourless oil as a mixture of *E*:*Z* isomers in >20:1 ratio (18.1 mg, 0.061 mmol, 84%).

ν_{max}/cm^{-1} 2956 m 2925 s 2854 s (C-H), 1601 w (C=C), 1457 m (alkyl C-H bend); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98 (d, *J* = 14.8 Hz, 1H, CH=C<u>H</u>S), 5.63 (dd, *J* = 14.8, 9.2 Hz, 1H, C<u>H</u>=CHS), 2.10 – 1.93 (m, 1H, C<u>H</u>CH=CHS), 1.32 (s, 9H, C(C<u>H</u>$_3$)$_3$), 1.47 – 1.08 (m, 26H, alkyl CH_2), 0.87 (t, *J* = 6.7 Hz, 6H, 2 × CH_2C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8 (CH), 119.1 (CH), 44.0 (CH), 43.7 (C), 35.4 (CH_2), 32.0 (CH_2), 30.9 (CH_3), 29.5 (CH_2), 27.4 (CH_2), 22.8 (CH_2), 14.3 (CH_3). Found (APCI) $[M+H]^+$ 299.2771, $C_{19}H_{39}S$ requires 299.2767.

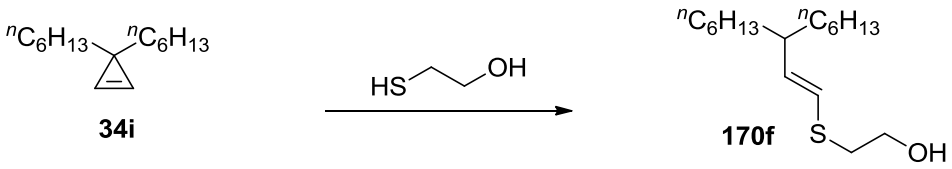
(*E*)-2-(((3-Hexylnon-1-en-1-yl)thio)methyl)furan **170e**:



Cyclopropene **34i** (15.0 mg, 0.072 mmol) was dissolved in DCM (0.30 mL). Catalyst **1** (3.0 mg, 0.0039 mmol) was added to a separate vial and dissolved in DCM (0.42 mL). Furfuryl mercaptan (7.3 µL, 8.2 mg, 0.072 mmol) was added to the vial using a Hamilton syringe. The mixture from the vial was then immediately transferred to cyclopropene **34i** *via* syringe. The reaction was allowed to stir at 25 °C for 1 hour, then the crude mixture was filtered through a short plug of silica using 10:1 hexane:diethyl ether. The desired product was purified using flash column chromatography (hexane → 50:1 hexane:diethyl ether), to yield **170e** as a yellow oil (20.3 mg, 0.063 mmol, 86%).

ν_{max}/cm^{-1} 2957 m 2922 s 2854 m (C-H), 1594 w (C=C), 1503 m 1458 m (Aromatic ring vibrations) 1010 s (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 1.9, 0.8 Hz, 1H, H_a), 6.29 (dd, *J* = 3.2, 1.9 Hz, 1H, H_b), 6.18 (dd, *J* = 3.2, 0.8 Hz, 1H, H_c), 5.84 (d, *J* = 15.0 Hz, 1H, CH=C<u>H</u>S), 5.45 (dd, *J* = 15.0, 9.2 Hz, 1H, C<u>H</u>=CHS), 3.83 (s, 2H, SC<u>H$_2$</u>C), 2.03 – 1.90 (m, 1H, C<u>H</u>CH=CH), 1.45 – 1.07 (m, 20H, alkyl CH_2), 0.88 (t, *J* = 6.8 Hz, 6H, 2 × CH_2C<u>H$_3$</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.6 (C), 142.2 (CH), 138.9 (CH), 120.8 (CH), 110.5 (CH), 107.6 (CH), 43.9 (CH), 35.4 (CH_2), 32.0 (CH_2), 30.2 (CH_2), 29.6 (CH_2), 27.3 (CH_2), 22.8 (CH_2), 14.3 (CH_3). Found (APCI) $[M+H]^+$ 323.2405, $C_{20}H_{35}OS$ requires 323.2403.

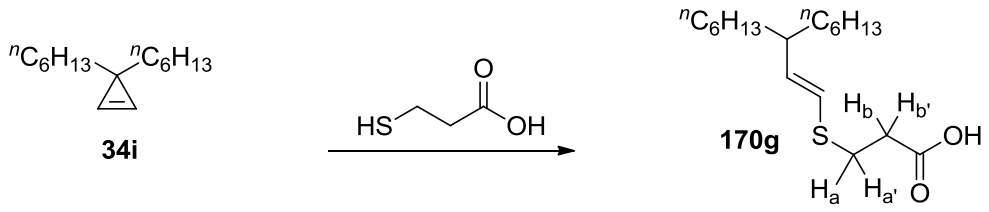
(*E*)-2-((3-Hexylnon-1-en-1-yl)thio)ethanol **170f**:



Cyclopropene **34i** (15.1 mg, 0.072 mmol) was dissolved in DCM (0.30 mL). Catalyst **1** (2.8 mg, 0.0036 mmol) was added to a separate vial and dissolved in DCM (0.42 mL). Mercaptoethanol (5.0 µL, 5.6 mg, 0.072 mmol) was added to the vial using a Hamilton syringe. The mixture from the vial was then immediately transferred to cyclopropene **34i** *via* syringe. The reaction was allowed to stir at 25 °C for 3 hours, then the crude mixture was filtered through a short plug of silica using 10:1 hexane:diethyl ether. The desired product was purified using flash column chromatography (hexane → 2:1 hexane:diethyl ether), to yield **170f** as a colourless oil as a mixture of *E*:*Z* isomers in >20:1 ratio (17.1 mg, 0.060 mmol, 82%).

ν_{max}/cm^{-1} 3400-3200 br. w (O-H), 2955 m 2921 s 2854 s (C-H), 1606 w (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (d, *J* = 15.0 Hz, 1H, CH=C<u>H</u>S), 5.51 (dd, *J* = 15.0, 9.1 Hz, 1H, C<u>H</u>=CHS), 3.81 – 3.71 (m, 2H, $CH_2C\underline{H_2}OH$), 2.83 (t, *J* = 5.9 Hz, 2H, $SC\underline{H_2}CH_2$), 2.12 – 1.90 (m, 2H, O<u>H</u> & C<u>H</u>CH=CH), 1.40 – 1.08 (m, 20H, alkyl CH_2), 0.87 (t, *J* = 6.7 Hz, 6H, 2 × $CH_2C\underline{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2 (CH), 120.4 (CH), 60.7 (CH_2), 43.9 (CH), 36.5 (CH_2), 35.3 (CH_2), 32.0 (CH_2), 29.5 (CH_2), 27.4 (CH_2), 22.8 (CH_2), 14.3 (CH_3). Found (APCI) $[M+H]^+$ 287.2406, $C_{17}H_{35}OS$ requires 287.2403.

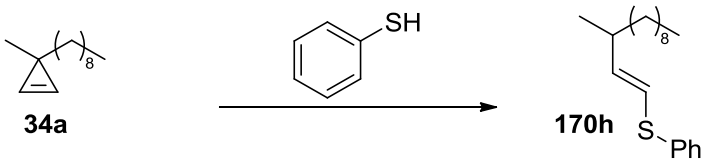
(*E*)-3-((3-Hexylnon-1-en-1-yl)thio)propanoic acid **170g**:



Cyclopropene **34i** (15.0 mg, 0.072 mmol) was dissolved in DCM (0.30 mL). Catalyst **1** (2.8 mg, 0.0036 mmol) was added to a small vial and dissolved in DCM (0.42 mL). 3-Mecaptopropionic acid (6.3 µL, 7.6 mg, 0.072 mmol) was added to the vial using a Hamilton syringe. The mixture from the vial was then immediately transferred to cyclopropene **34i** *via* syringe. The reaction was allowed to stir at 25 °C for 2 hours. The desired product was purified using flash column chromatography (hexane → 2:1 diethyl ether:hexane), to yield **170g** as a colourless oil as a mixture of *E*:*Z* isomers with a ratio of >20:1 (16.5 mg, 0.052 mmol, 73%).

ν_{max}/cm^{-1} 3100-2700 br. w (O-H), 2956 m 2924 s 2854 s (C-H), 1711 s (C=O), 1604 w (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.78 – 9.74 (br s, 1H, OH), 5.80 (d, *J* = 15.0 Hz, 1H, CH=C<u>H</u>S), 5.46 (dd, *J* = 15.0, 9.1 Hz, 1H, CHC<u>H</u>=CHS), 2.88 (t, *J* = 7.0 Hz, 2H, $H_{a/a'}$/$H_{b/b'}$), 2.69 (t, *J* = 7.0 Hz, 2H, $H_{a/a'}$/$H_{b/b'}$), 2.08 – 1.91 (m, 1H, C<u>H</u>CH=CHS), 1.41 – 1.10 (m, 20H, alkyl CH_2), 0.87 (t, *J* = 6.7 Hz, 6H, 2 × C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2 (C), 139.0 (CH), 120.5 (CH), 43.9 (CH), 35.4 (CH_2), 34.5 (CH_2), 32.0, (CH_2) 29.5 (CH_2), 27.6 (CH_2), 27.4 (CH_2), 22.8 (CH_2), 14.3 (CH_3). Found (ESI) $[M-H]^-$ 313.2198, $C_{18}H_{33}O_2S$ requires 313.2207.

(*E*)-(3-Methyldodec-1-enyl)(phenyl)sulfane **170h**:

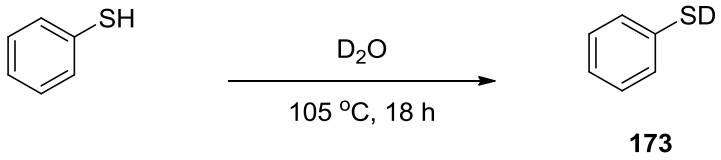


Cyclopropene **34a** (203.5 mg, 1.12 mmol) was in DCM (6 mL). Catalyst **1** (42.5 mg, 0.055 mmol) was added to a small vial and dissolved in DCM (5 mL). Thiophenol (114 µL, 122.2 mg, 1.12 mmol) was added to the vial. The mixture from the vial was then immediately transferred to cyclopropene **34a** *via* syringe. The reaction was allowed to stir at 25 °C for 30 min. The desired product was purified using flash column chromatography (50:1 hexane:diethyl ether), to yield **170h** as a colourless oil (255.7 mg, 0.88 mmol, 78%).

ν_{max}/cm^{-1} 2970 s (C-H), 2922 s (C-H), 1583 w (C=C), 1454 m, 1439 m (Ar C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 – 7.39 (m, 5H, Ar-H), 6.13 (d, *J* = 15.0 Hz, 1H, CHCH=C<u>H</u>S), 5.93 (dd, *J* = 15.0, 7.9 Hz, 1H, CHC<u>H</u>=CHS), 2.21 – 2.41 (m, 1H, C<u>H</u>CH=CHS), 1.16 – 1.44 (m, 16H, alkyl CH_2), 1.07 (d, *J* = 6.6 Hz, 3H, CHC<u>H</u>$_3$), 0.90 (t, *J* = 6.6 Hz, 3H, CH_2C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8 (CH), 136.8 (C), 128.9 (CH), 128.3 (CH), 125.9 (CH), 119.0 (CH), 37.6 (CH), 36.8 (CH_2), 31.9 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.4 (CH_2), 27.4 (CH_2), 22.7 (CH_2), 20.4 (CH_3), 14.2 (CH_3); Found (APCI) $[M+H]^+$ 291.2142, $C_{19}H_{31}S$ requires 291.2141.

Deuterium labelling study:

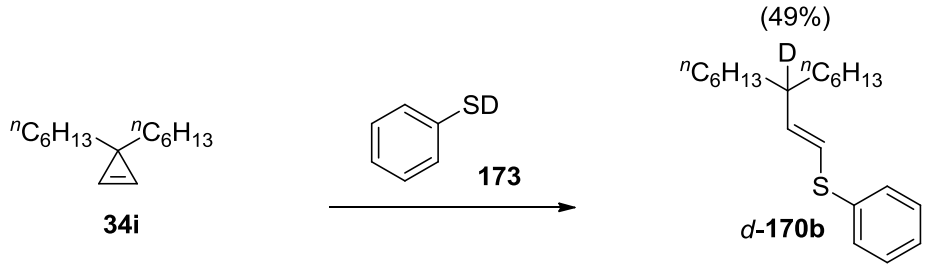
S-Deuterothiophenol **173**:[41]



173

A solution of thiophenol (0.54 g, 4.90 mmol) in D_2O (1 mL) was heated to reflux overnight under an atmosphere of argon, with vigorous stirring. The reaction was then cooled to room temperature and the product was extracted with hexane (3 x 5 mL), then dried over Na_2SO_4 and concentrated under reduced pressure. Analysis by ^1H NMR in $CDCl_3$ indicated that thiophenol was 77% deuterium-enriched at the *S*-position.

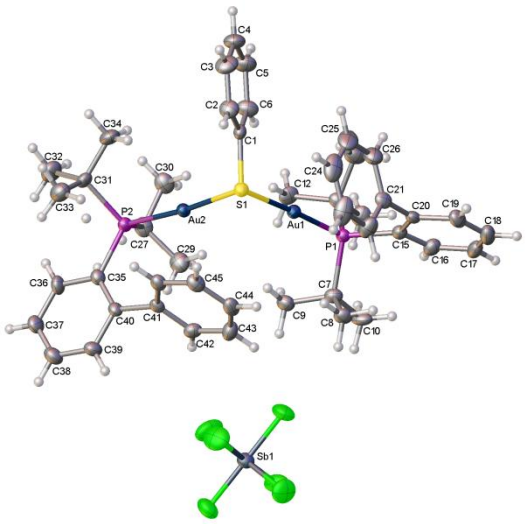
(E)-(3-Deutero-3-hexylnon-1-en-1-yl)(phenyl)sulfane *d*-**170b:**

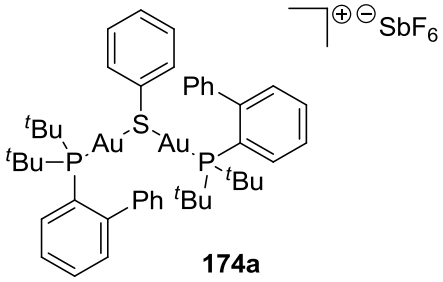


Deuterated thiophenol **173** (7.4 µL, 7.9 mg, 0.072 mmol) was added via syringe to a solution of catalyst **1** (2.9 mg, 0.0038 mmol) in dry DCM (0.42 mL). The resulting solution was transferred immediately to a solution of cyclopropene **34i** in dry DCM (0.30 mL) via syringe. The reaction was stirred at 25 °C for 30 min under argon, then the mixture was filtered through a short silica plug using 10:1 hexane:diethyl ether. Analysis of ^{1}H NMR spectrum showed that further purification was not necessary. The deuterated product *d*-**170b** was obtained as a colourless oil (14.9 mg, 0.047 mmol, 65%). Analysis of the ^{1}H NMR shows that *d*-**170b** was obtained as one product with approximately 49% deuterium incorporation. Analysis of the HRMS data indicates that *d*-**170b** was obtained with 55% ± 10% deuterium incorporation.

ν_{max}/cm^{-1} 2955 m 2923 s 2854 s (C-H), 2163 w (C-D), 1679 w (C=C), 1584 m 1479 m (Ar C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 4H, Ph H), 7.23 – 7.14 (m, 1H, Ph H), 6.07 (d, *J* = 14.9 Hz, 1H, CH=C<u>H</u>S), 5.76 (dd, *J* = 14.9, 9.2 Hz, 1H, CHC<u>H</u>=CHS from non-deuterated product), 5.76 (d, *J* = 14.9 Hz, 1H, CDC<u>H</u>=CHS), 2.17 – 2.06 (m, 1H, C<u>H</u>CH=CHS from non-deuterated product), 1.47 – 1.13 (m, 20H, alkyl CH_2), 0.89 (t, *J* = 6.6 Hz, 6H, 2 × $CH_2C\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.13 (CH non-deuterated), 143.10 (CH deuterated), 137.1 (C), 129.0 (CH), 128.3 (CH), 126.0 (CH), 120.09 (CH non-deuterated), 120.07 (CH deuterated), 43.9 (CH non-deuterated), 43.4 (t, *J* = 19.1 HZ, CD), 35.3 (CH_2 non-deuterated), 35.2 (CH_2 deuterated), 32.0 (CH_2), 29.5 (CH_2), 27.5 (CH_2 non-deuterated), 27.4 (CH_2 deuterated), 22.8 (CH_2), 14.3 (CH_3); Found (EI) $[M]^+$ 319.2434, $C_{21}H_{33}DS$ requires 319.2439.

Complex 174a:





174a

Thiophenol (2.8 mg, 2.7 μL, 0.026 mmol) was added to a solution of catalyst **1** (20 mg, 0.026 mmol) in DCM (0.70 mL). Single crystals were grown from slow evaporation of the DCM solution. M.p. 184 °C (decomposes); ν_{max}/cm^{-1} 2951 m 2886 w (C-H), 1577 m 1469 m 1440 m (Aromatic C=C); ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.93 – 7.84 (m, 2H), 7.62 – 7.45 (m, 6H), 7.35 – 7.16 (m, 11H), 7.15 – 7.09 (m, 4H), 1.37 (d, $J(^{1}H–^{31}P)$ = 15.8 Hz, 36H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 149.8 (d, $J(^{13}C–^{31}P)$ = 14.2 Hz, C), 143.3 (d, $J(^{13}C–^{31}P)$ = 6.7 Hz, C), 134.4 (CH), 133.73 (d, $J(^{13}C–^{31}P)$ = 7.6 Hz, CH), 133.72 (CH), 131.7 (CH), 129.9 (CH), 129.7 (CH), 129.3 (CH), 129.2 (CH), 128.5 (CH), 128.1 (CH), 128.0 (CH), 127.8 (C), 127.5 (CH), 125.8 (d, $J(^{13}C–^{31}P)$ = 44.3 Hz, C), 38.5 (d, $J(^{13}C–^{31}P)$ = 23.7 Hz, C), 31.3 (d, $J(^{13}C–^{31}P)$ = 6.9 Hz, CH_3); ^{31}P NMR (121 MHz, CD_2Cl_2) δ 62.87. Crystal Data. $C_{46}H_{59}Au_2F_6P_2SSb$, M =1335.61, monoclinic, a = 24.6918(3) Å, b = 13.08924(15) Å, c = 29.3558(4) Å, β = 90.7654(11)°, V = 9486.84(19) $Å^3$, T = 120.01(10), space group Cc (no. 9), Z = 8, μ(Cu Kα) = 17.388, 77919 reflections measured, 19283 unique (R_{int} = 0.0447) which were used in all calculations. The final wR_2 was 0.0820 (all data) and R_1 was 0.0313 (>2σ(I)).

CCDC deposition number: 896069

3.6 References

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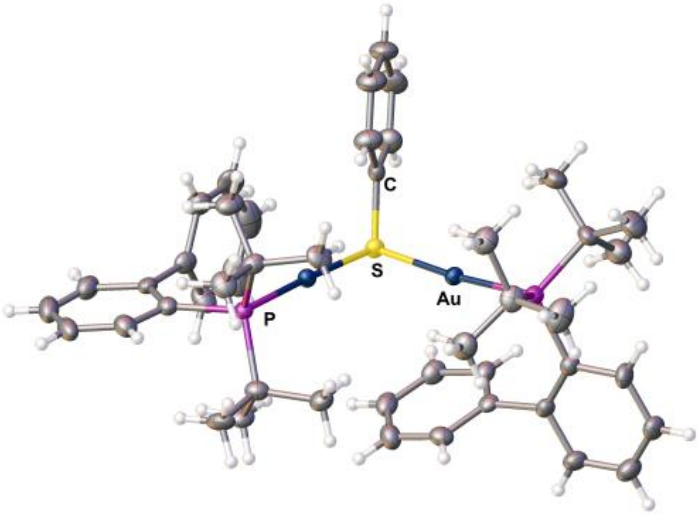
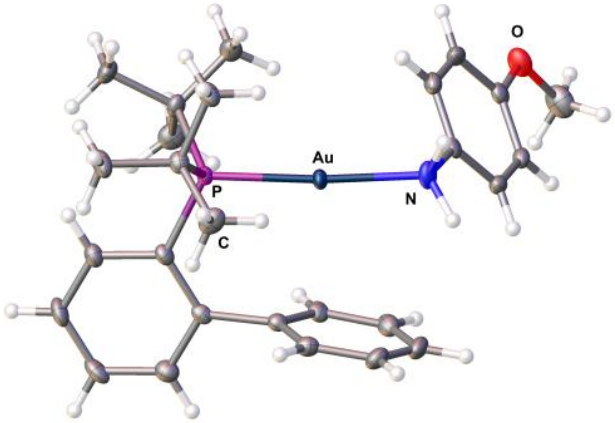
Chapter 4 – Deactivation of Gold(I) Catalysts in the Presence of Thiols and Amines





Acknowledgements – The author is grateful for the contribution by Samantha Green (MChem project student) towards this chapter (initial preparations of **174a-c** & Table 4.3, entries 1-3).

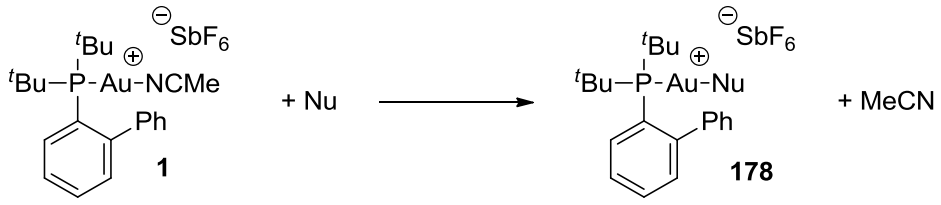
4.1 Introduction

The efforts over the past decade in the area of gold(I) catalysis have shown the vast array of reactions that are possible, with the ability to build complex structures under (generally) mild reaction conditions.[1-21] More recently, however, there has been an increasing amount of work focused on the reaction mechanisms, and the gold-species that are actually involved in the transformations.

The species being formed in gold(I)-catalysed reactions can help explain reactivity and selectivities, hence probing these species is vitally important in furthering the overall understanding of gold(I) catalysis. Both the substrate being activated, as well as the reacting nucleophile can alter the activity and efficacy of the gold(I) catalyst, and the selection of reactants must be considered before use due to potential catalyst deactivation.

An in-depth NMR study into the nature of the gold(I)-catalysts in solution with various nucleophiles was reported in 2012 by Maier.[22] Various nucleophiles were added to different gold(I) catalysts in solution to determine if the nucleophile would change the overall structure of the gold(I) species. The study involved gold(I) catalysts with a range of ligands including; phosphine, phosphite, NHCs as well as binuclear gold complexes.

Maier and co-workers utilised Echavarren's catalyst **1** for a large part of their studies due to its labile acetonitrile ligand.[23] On the addition of nucleophiles, the authors monitored the position of the MeCN peak in the ^{1}H NMR spectra in order to determine when ligand exchange had occurred (free MeCN was observed at 2.00 ppm in $CDCl_3$) (Scheme 4.1). From screening a large range of nucleophiles and calculating their equilibrium constant by NMR, the relative ligand strength could be determined for catalyst **1** (Scheme 4.2).



Scheme 4.1. Reaction of catalyst **1** with nucleophiles.

MeOH 3-hexyne MeCN OTf^- Me_2S Lut Pic $OTFA^-$ DMAP

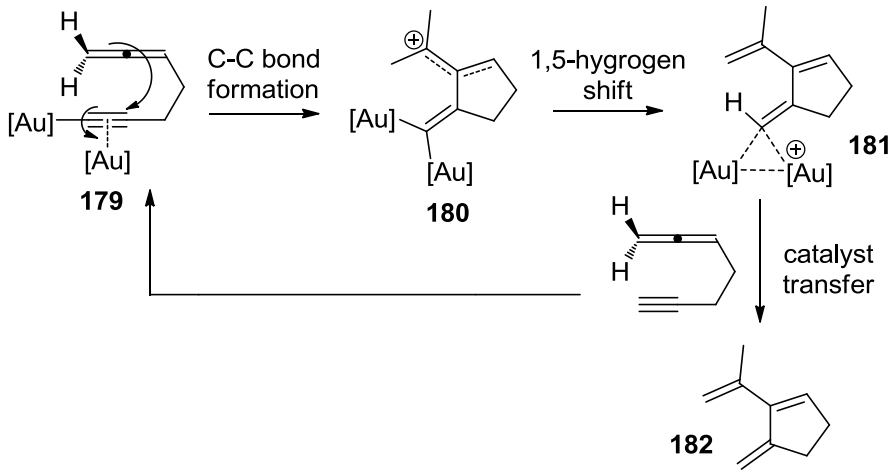
TMTU PPh_3 Cl OH

Scheme 4.2. Ligand strength series for catalyst **1**.

All added substrates were found to displace MeCN from the parent gold(I) catalyst, excluding MeOH and 3-hexyne. Ligand exchange with methanol only occurred in neat MeOD solution, demonstrating that it is an extremely weak ligand for gold(I). 3-Hexyne (a strongly binding alkyne to gold(I) species)[24] was found to be unsuccessful in displacing the MeCN ligand, with the binding to gold(I) being weaker than MeCN by a factor of 10-100. The authors suggest that this provides an reasonable explanation as to why using acetonitrile as a solvent in gold(I)-catalysed reaction generally results in poor reactivity.

All other ligands were shown to displace the acetonitrile ligand from the parent catalyst **1**, to form the resulting complex **178**. All these complexes were solely studied by NMR in solution, no attempts were made to isolate and characterise them. Therefore from this study, no conclusions can be drawn about the catalytic abilities of these gold-nucleophile complexes **178** in gold(I)-catalysed reactions.

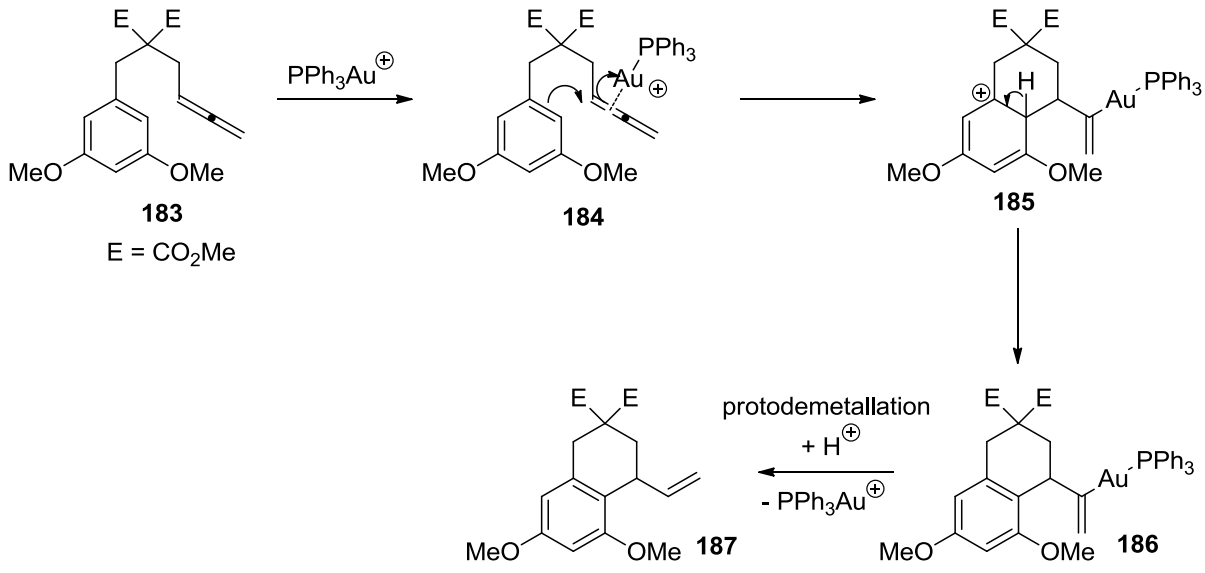
In the area of isolating and characterising gold species along the catalytic pathway, recent literature has revealed the importance of *gem*-digold species in catalytic cycles. A few selected reports on *gem*-digold species will be highlighted herein. A study by Toste and co-workers in 2008 was the first to report evidence of the formation of *gem*-digold complexes.[25] During the mechanistic studies of their reaction, the authors found that the *gem*-diaurated species could form along the reaction pathway (Scheme 4.3).



Scheme 4.3. Catalytic cycle with formation of *gem*-digold species by Toste.

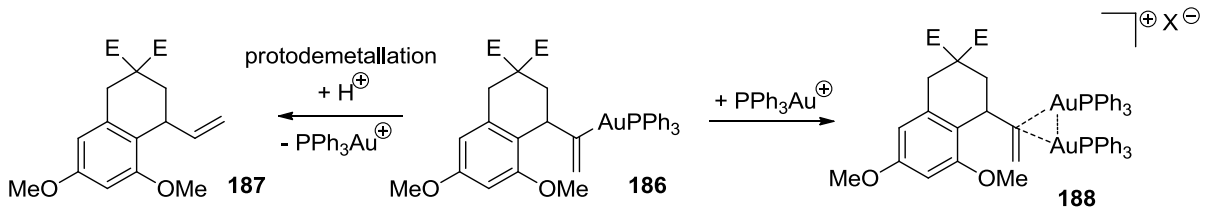
Toste proposed that the reaction is initiated by a dual σ,π-activation of the allene-yne substrate, giving intermediate **179**. After the C-C bond formation and 1,5-hydrogen shift, the *gem*-digold species **181** is formed. The desired product **182** is released after catalyst transfer with another molecule of allene-yne substrate (which reforms species **179**). This initial report inspired many other research groups to investigate the nature of these *gem*-digold complexes, and elucidate on their role in the mechanism of gold(I)-catalysed reactions.[26-32]

Gagné and co-workers studied the formation of a *gem*-digold species with respect to the overall reaction mechanism.[28-30] The gold(I)-catalysed intramolecular hydroarylation of allenes was investigated and the authors put forward their proposed mechanism (Scheme 4.4).[29, 30] The gold(I) catalyst activates allene substrate **183**, activating it toward intramolecular nucleophilic attack (**184**) from the aromatic ring. Species **186** is formed after rearomatisation, which delivers the final product **187** after protodemetallation.



Scheme 4.4. Proposed mechanism for the gold(I)-catalysed hydroarylation of allenes.

The mechanistic studies carried out by the authors showed that another pathway could be followed from species **186** (Scheme 4.5). The desired product **187** is afforded *via* protodemetallation of species **186**, however *gem*-digold species **188** was also observed as a stable complex. Species **188** is formed by the second addition of gold(I)-catalyst to **186**. The authors state that this step is in competition with the protodemetallation process, and therefore hinders the formation of the desired product **187**.

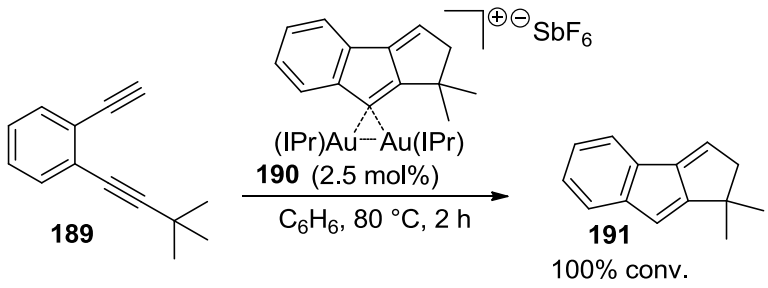


Scheme 4.5. Competitive pathways from species **186**.

Furthermore, it was found that *gem*-digold species **188** is more stable than monogold complex **186**. This resulted in the active gold(I) catalyst being sequestered much quicker than the catalyst could activate the allene substrate. It has been suggested that this *gem*-digold species is perhaps an off-cycle reservoir of gold(I)-catalyst, or the catalyst's resting state.[28, 30]

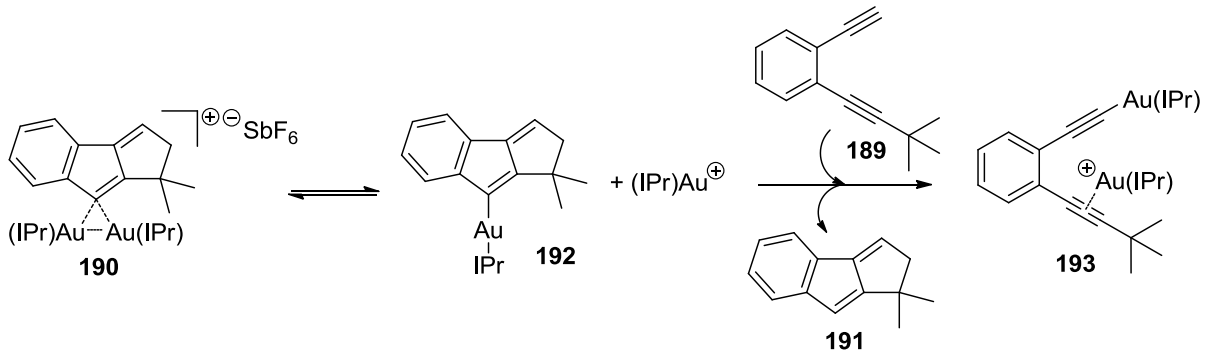
The nature of the counterion appeared to have a large influence on the formation of the *gem*-digold complex **188**.[30] The catalysts with the least coordinating counterions (e.g. NTf_2^-) were more prone to forming *gem*-digold complexes. In the context of catalysis, counterions that are less coordinating tend to be favoured as the gold(I)-centre has increased reactivity toward substrate activation. However, on selecting these less coordinating counterions, the propensity to form more stable, less reactive *gem*-digold species is increased. Therefore, a balance has to be reached for efficient catalysis.

Interestingly, a report by Hashmi and co-workers demonstrated that a *gem*-digold species could act as an excellent, and more efficient catalyst compared to a standard commercially available complex (Scheme 4.6).[31]



Scheme 4.6. *Gem*-digold complex catalysed formation of benzofulvene.

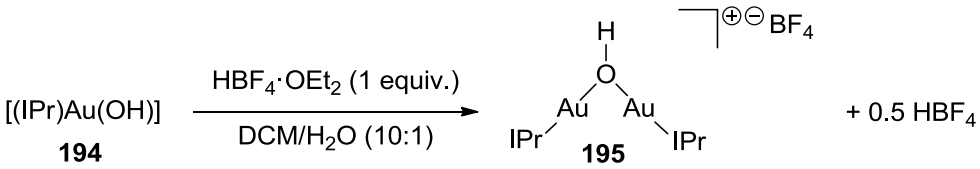
The gold(I)-catalysed transformation of diyne **189** to benzofulvene **191** was found to be three times faster with complex **190** than with the standard catalyst system [(IPr)AuSbF$_6$ prepared *in situ*]. Scheme 4.7 highlights how the authors propose that species **190** is in equilibrium with monogold complex **192** and active cationic gold(I) catalyst $[(IPr)Au]^+$; these are the two species required to carry out the catalytic cycle. The monogold complex **192** undergoes protodemetallation and forms product **191** and the σ-activated alkyne-gold bond after addition of diyne substrate **189**, whereas the cationic gold(I) species will perform the π-activation on the second alkyne **193**. Since the *gem*-digold species **190** is in equilibrium with the two components needed for catalysis, the authors suggest this is the rationale behind why the reaction is three times faster (2 hours *vs.* 6 hours) with species **190**, compared to (IPr)AuSbF$_6$. However, it is important to note that this remains true solely because this reaction requires σ,π-type dual activation of the substrate. In cases which require solely π-type activation, the *gem*-digold species would presumably be detrimental to the catalytic cycle.



Scheme 4.7. Mechanistic rationale for the increased reactivity observed with **190** as the catalyst.

Currently, it is still unclear what the overall role of these *gem*-digold species in gold(I) catalysis is, due to the lack of research carried out in this area.[26] However, recently there has been growing interest in *gem*-digold species. The Nolan Group have demonstrated that structurally similar *gem*-digold species with a bridging hydroxy ligand can be used as efficient catalysts.[33, 34]

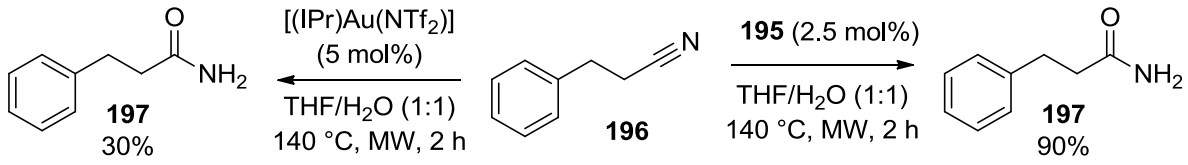
Formation of the digold species **195** was achieved by addition of an acid to parent catalyst [(IPr)Au(OH)] **194**. The authors state that water assists in the formation of **195**, and although it can form in the presence of dry solvent, there are other gold(I) species observed. However, when "wet" solvent is used, the sole product is complex **195.**



Scheme 4.8. Formation of digold species with bridging hydroxy ligand.

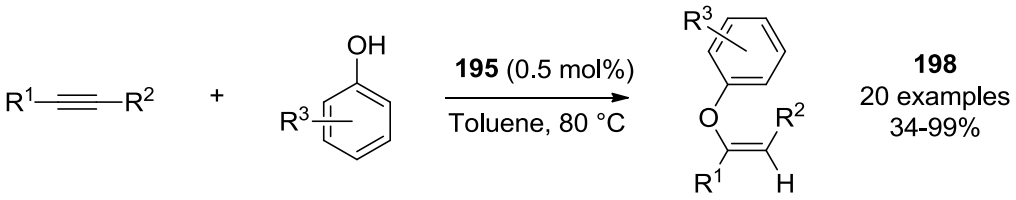
Having determined a method of synthesising species **195**, Nolan and co-workers proceeded to test its catalytic ability in a range of gold(I)-catalysed reactions.[33] A comparison was carried out between these digold species **195** and a more standard gold(I) catalyst [(IPr)Au(NTf_2)] (Scheme 4.9). It was shown that nitrile **196** can undergo hydration to the amide **197** more effectively using the digold species **195**, compared to a standard catalyst system (90% *vs.* 30%). Although their study was short, it demonstrated that in certain cases the digold complex **195** was indeed a better choice

of catalyst compared to the standard gold(I) catalyst systems currently used throughout the literature.

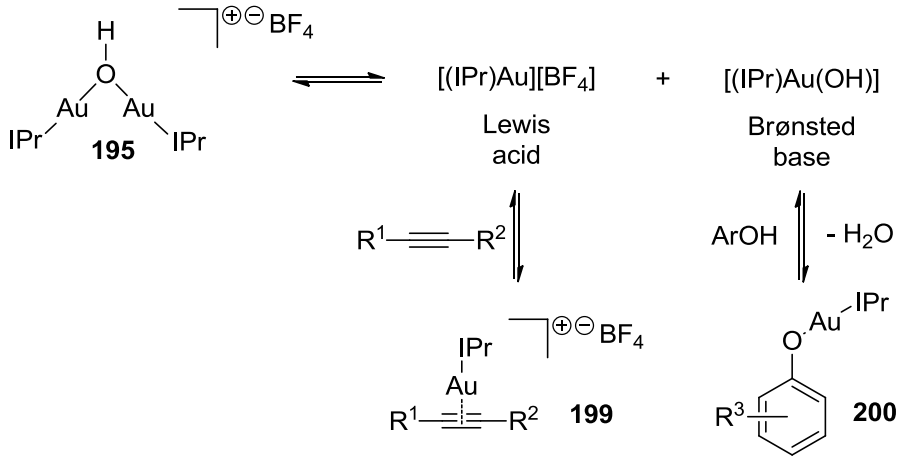


Scheme 4.9. Comparison of digold species **195** and standard gold(I) catalyst system by Nolan.

The Nolan group expanded on their investigations into complex **195** showing that the species could catalyse the hydrophenoxylation of alkynes, yielding vinyl ethers **198** (Scheme 4.10).[35] The authors propose that the reaction proceeds *via* a cooperative/dual catalysis pathway, with complex **195** in equilibrium with a Lewis acid [(IPr)Au][BF_4] and Brønsted base [(IPr)Au(OH)], both of which can activate separate substrates (Scheme 4.11). The Lewis acid component can activate the alkyne substrate toward nucleophilic attack (**199**), whereas the Brønsted base unit can react with the phenol to form a gold-phenoxide complex **200**, which can successfully attack the activated alkyne **199**.



Scheme 4.10. Gold(I)-catalysed hydrophenoxylation of alkynes by Nolan.

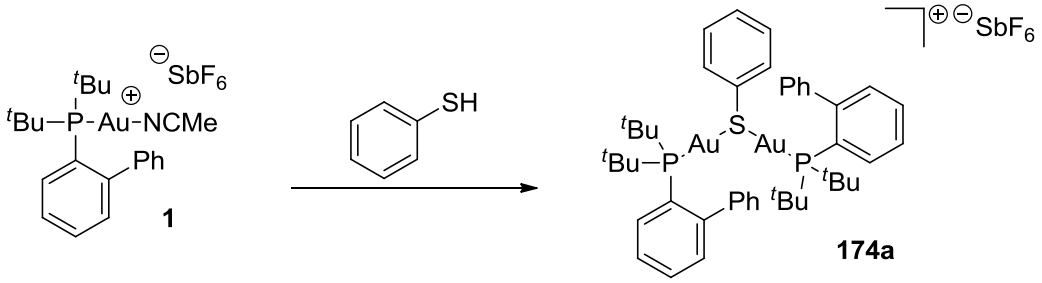


Scheme 4.11. Dissociation of **195** to enable cooperative/dual catalysis.

Although digold species with bridging carbon or oxygen such as **190** and **195** have been studied in the context of catalysis, the bridging thiolate equivalents (see **174a**, Chapter 3) have not. This chapter thus details our efforts in characterising these digold thiolate species, as well as investigating their effect in catalytic reactions.

4.2 Project Aims

Studies into the mechanism of the gold(I)-catalysed thiol addition to cyclopropenes revealed that a digold species with bridging thiolate was formed on the addition of thiophenol to gold(I) catalyst **1** (Chapter 3) (Scheme 4.12).[36]

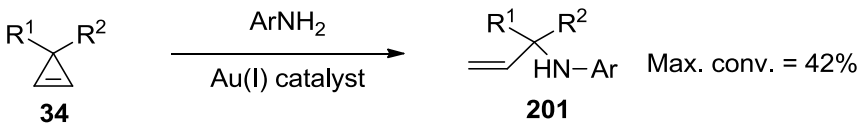


Scheme 4.12. Formation of digold species with bridging thiolate.

It was proposed that this type of species could account for the deactivation of the gold(I) catalyst, therefore further studies to elaborate on these findings were desired, focussing on sulfur- and amine-based nucleophiles with gold(I) catalyst **1**. Screens of these nucleophiles were to be undertaken in order to determine if each would result in structures similar to **174a**.

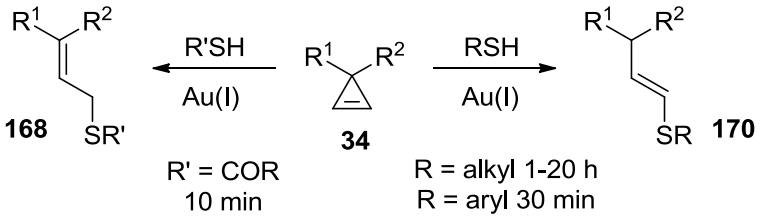
Once the nature of the gold-nucleophile complexes had been identified, investigations into their catalytic abilities were to be probed. Known reactions were to be tested in order to compare their abilities against one another, but also in the hope of explaining why certain reactions do not proceed to completion.

Previous work in the Lee Group showed that anilines can react with cyclopropenes **34** to afford tertiary allylic amines **201** (Scheme 4.13).[37] However, the reactions were found to never proceed with full conversion from the starting material substrate (maximum conversion = 42%). This is presumably due to the catalyst being deactivated by the amine nucleophile, hence suppressing the activity of the gold(I) species. Studies into the deactivated species being formed were to be carried out, followed by how this species fares as a catalyst in the amine addition reaction.



Scheme 4.13. Gold(I)-catalysed aniline addition to cyclopropenes.

Alternatively, when thiols and thioacids are used as nucleophiles, the reaction does successfully proceed to completion (Scheme 4.14). However, a notable decrease in reactivity was observed when more nucleophilic sulfur nucleophiles were used; thioacids require 10 minutes, alkylthiols require up to 20 hours reaction time. The mechanism of formation of the digold species with bridging thiolate was to be explored, followed by studies on whether these complexes are catalytically active.



Scheme 4.14. Gold(I)-catalysed addition of sulfur nucleophiles to cyclopropenes.

4.3 Results & Discussion

4.3.1 Gold(I) catalyst with thiols, thiophenols & thioacids

The preliminary result obtained while studying the mechanism of the gold(I)-catalysed thiol addition to cyclopropenes showed that digold species with bridging thiolate **174a** is isolated when thiol is added to **1** (Chapter 3, Section 3.3.2). In order to compare other *S*-nucleophiles, the same procedure was undertaken to investigate the changes in the parent gold(I) catalyst.

Echavarren's gold(I) catalyst **1**[23] was selected for the studies due to its labile MeCN ligand. During the formation of complex **174a**, the MeCN is displaced on addition of thiophenol and can be observed by ^{1}H NMR spectroscopy. Therefore, following this procedure a small screen of *S*-nucleophiles was performed. Initially, the sulfur nucleophiles were added to catalyst **1** at a ratio of 20:1, mimicking the reaction conditions used in thiol additions to cyclopropenes. All reactions were analysed by ^{1}H and ^{31}P NMR spectroscopy to view any changes to the parent catalyst **1** (Figure 4.1).

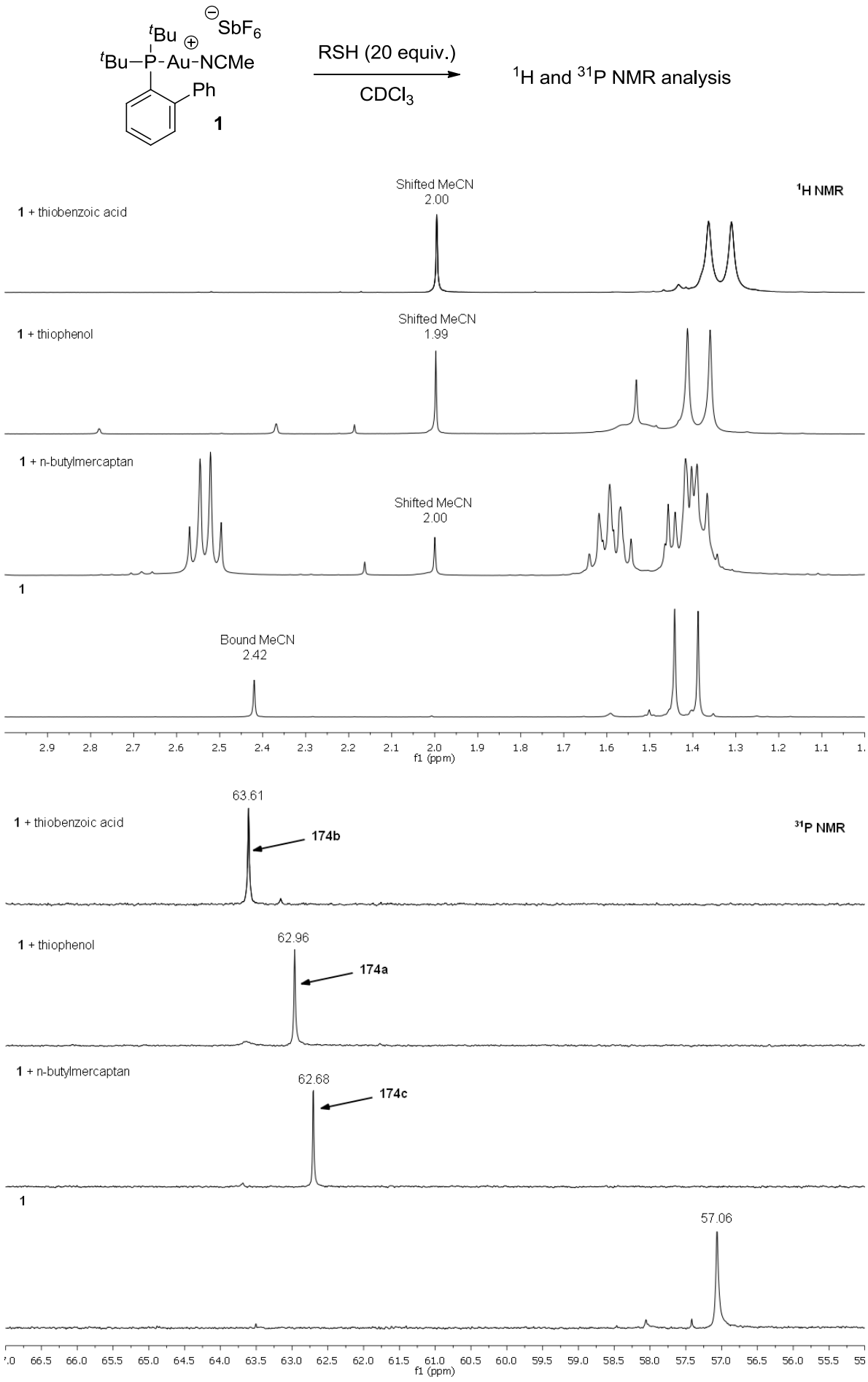


Figure 4.1. ^{1}H and ^{31}P NMR analysis of 20:1 *S*-nucleophile:**1**.

Figure 4.1 clearly demonstrates that the chemical shift of the MeCN peak on the parent catalyst shifts significantly on the addition of each *S*-nucleophile (Figure 4.1, top spectra). Addition of thiobenzoic acid, thiophenol and *n*-butylmercaptan to **1** all result in unbound MeCN ligand (moving from 2.42 ppm to 2.00 ppm), suggesting that it has been displaced by the sulfur nucleophile.

The change in structure was also confirmed by a shift in the phosphine ligand peak in the ^{31}P NMR spectra (Figure 4.1, bottom spectra). Increasing the Lewis basicity of the *S*-nucleophile results in an upfield shift of the phosphine peak; with thiobenzoic acid, thiophenol and *n*-butylmercaptan showing a species with a shifted phosphine peak at 63.61, 62.96 and 62.68 ppm respectively. This upfield shift corresponds to an increasingly more electron rich metal centre.

In an attempt to isolate the structures being formed on addition of thiols, a 1:1 mixture of *S*-nucleophile:**1** was prepared. Once again, to confirm that a change in structure had occurred, ^{1}H and ^{31}P NMR spectra were obtained (Figure 4.2).

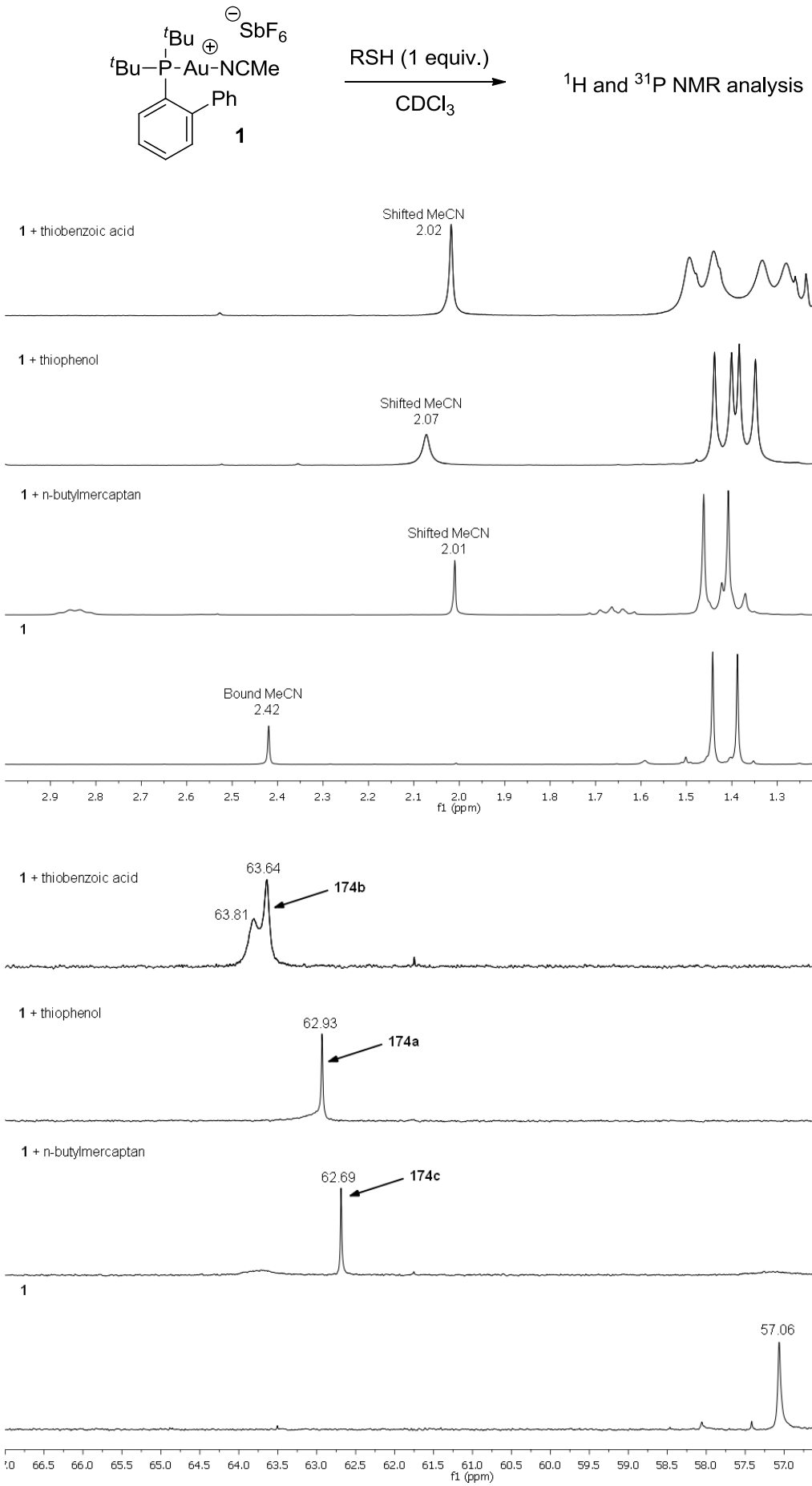
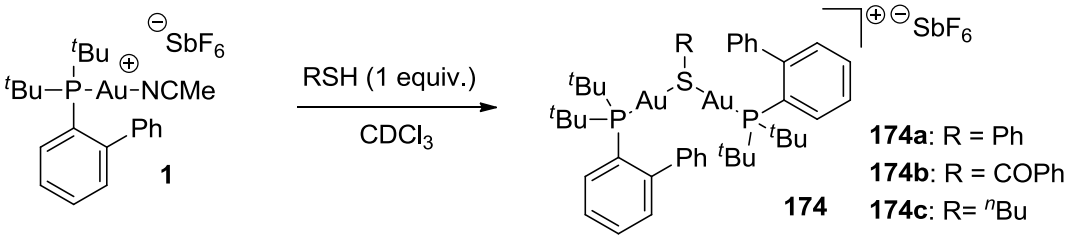


Figure 4.2. ^{1}H and ^{31}P NMR analysis of 1:1 *S*-nucleophile:**1**.

It is evident that there is still a definite shift in the MeCN peak on the addition of 1 equivalent of *S*-nucleophile (Figure 4.2, top spectra). Both thiobenzoic acid and *n*-butylmercaptan showed the peak appearing at 2.01 ppm, whereas after addition of thiophenol the peak shifted to 2.07 ppm. Although these vary slightly from the experiments with 20 equivalents of *S*-nucleophiles, it is still evident that a change in overall structure has occurred.

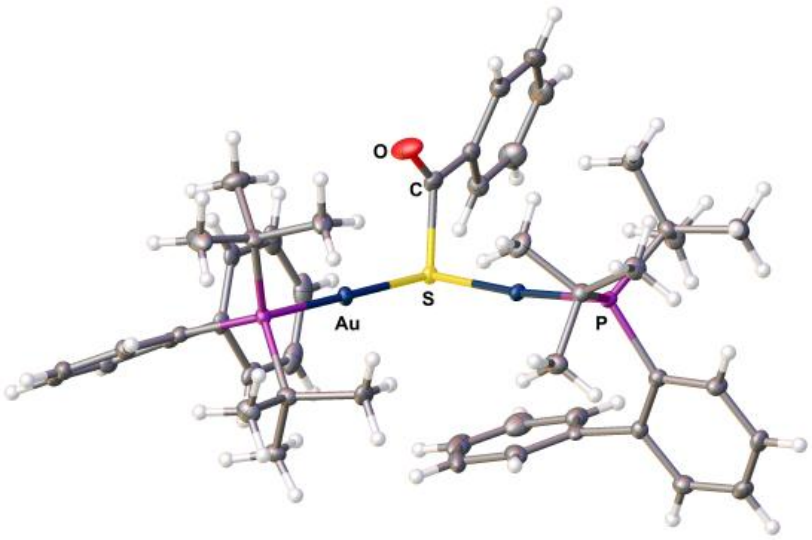
This change was, once again, confirmed by analysis of the ^{31}P NMR spectra (Figure 4.2, bottom spectra). Addition of thiophenol and *n*-butylmercaptan resulted in the phosphine ligand peak appearing at 62.93 and 62.69 ppm respectively. However, after addition of thiobenzoic acid to the parent catalyst **1**, two peaks are observed in the ^{31}P NMR spectrum. One of these peaks corresponds to that observed in the 20:1 experiment (Figure 4.2, bottom spectrum), whereas the second is an unidentified product.

In order to fully characterise these newly formed species, crystals were grown by vapour diffusion ($CDCl_3$/hexane), from the 1:1 mixture of *S*-nucleophile:**1**. Characterisation was obtained by X-ray crystallography, and all three examples contained the same digold species with bridging thiolate $[(Au(L))_2(\mu\text{-SR})][SbF_6]$ **174** (Scheme 4.15 & Figure 4.3). Structures **174b**, **174a** and **174c** were all fully characterised by ^{1}H, ^{13}C, ^{31}P NMR, IR and HRMS (See Section 4.5), and found to remain stable for over 3 months.

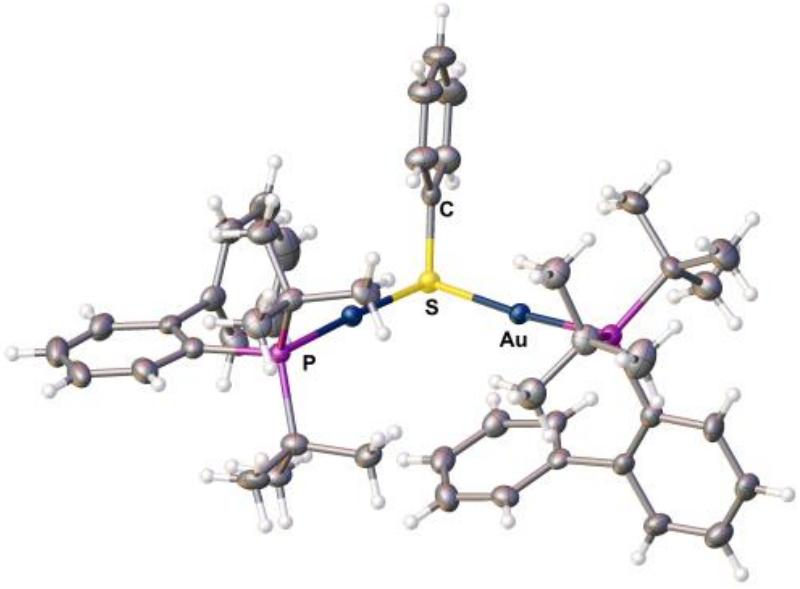


Scheme 4.15. Formation of digold species with bridging thiolate.

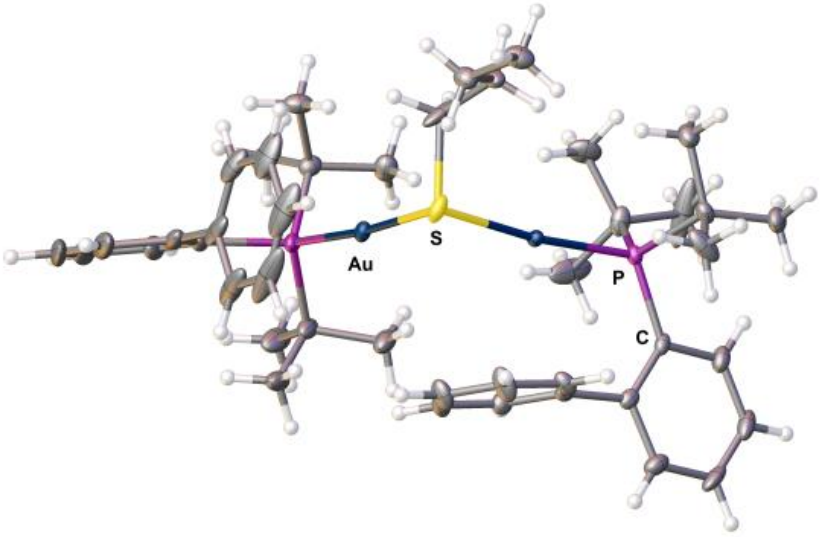
All structures showed no formal Au-Au bond, however the intramolecular Au-Au distances were found to be 3.3987(3), 3.4066(4) and 3.4363(3) Å for **174b**, **174a** and **174c** respectively, which suggests there is a degree of aurophilic interactions (accepted range *ca.* 2.85-3.50 Å).[38] Catalyst **1** is reported to have a weak gold(I)-arene interaction, which is suggested to stabilise the gold(I) centre.[23] A similar interaction is observed with the newly formed complexes, with Au-arene distances of 3.218/3.173, 3.212/3.183, 3.218/3.204 Å for **174b**, **174a** and **174c** respectively.



174b



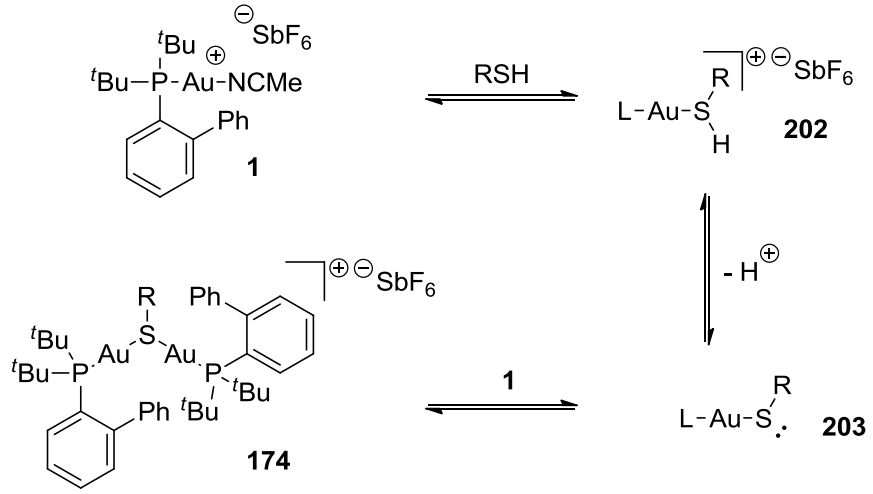
174a



174c

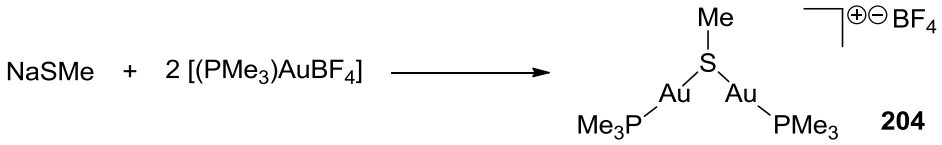
Figure 4.3. X-ray structures of **174b**, **174a** and **174c**. SbF_6^- counterion is omitted for clarity.

The proposed mechanism of formation of complexes **174a-c** is outlined in Scheme 4.16. The *S*-nucleophile displaces the MeCN ligand on the parent catalyst **1**, resulting in the formation of the cationic species **202**. Loss of a proton forms neutral species **203**, and this can react with another molecule of **1** through the lone pairs on the sulfur, yielding the observed product **174**. The route is thought to be reversible, and this along with catalytic studies will be discussed further in Section 4.3.3.



Scheme 4.16. Proposed mechanism for the formation of complex **174**.

It is worth noting that these types of digold structures with bridging thiolates are known in the literature.[39, 40] However these examples were prepared using basic conditions. For example, Schmidbaur demonstrated in 1996 that the complex **204** can be obtained from reacting NaSMe with [(PMe_3)$AuBF_4$] (Scheme 4.17).[39]



Scheme 4.17. Basic conditions used in the formation of **204** by Schmidbaur.

Since these studies all predate the explosion of interest in gold(I) complexes as catalysts, these early reports do not include any investigations on the catalytic properties of such species, or their role in catalytic cycles.

4.3.2 Gold(I) catalyst with amines and anilines

The formation of digold species with bridging thiolates **174a-c** raised the question of how *N*-nucleophiles would behave on addition to catalyst **1**. To investigate this, an analogous study was performed as described in Section 4.3.1, using catalyst **1** and 1 equivalent of a series of *N*-nucleophiles; aniline, *p*-anisidine and *n*-butylamine (Figure 4.4).

As observed with the series of *S*-nucleophiles, a definite shift of the MeCN peak in the ^{1}H NMR spectrum occurs on addition of the *N*-nucleophiles. All three nucleophiles resulted in an upfield shift of the MeCN peak from 2.42 ppm in the parent catalyst **1** to 2.01 ppm after amine addition (Figure 4.4, top spectra). This upfield shift suggests that the MeCN had become unbound from catalyst **1**, and a new complex had formed.

Similar trends were found in the ^{31}P NMR spectrum, with the phosphine ligand showing a change in its chemical shift (Figure 4.4, bottom spectra). Increasing the Lewis basicity of the amine from aniline – *p*-anisidine – *n*-butylamine resulted in the phosphine ligand signal appearing at 58.83, 58.70 and 58.32 ppm respectively. This upfield change in chemical shift for the phosphine ligand is expected for an increasingly electron rich metal centre.

In order to determine the structure of these gold complexes, crystals were grown by vapour diffusion ($CDCl_3$/hexane) from the 1:1 *N*-nucleophile:**1**. Crystals were obtained and their structures were determined by X-ray crystallography. The confirmed structures were very different to that with *S*-nucleophiles, with all three *N*-nucleophiles a monogold species [LAu-NH_2R][SbF_6] **205** is formed Scheme 4.18 & Figure 4.5). Structures **205a**, **205b** and **205c** were all fully characterised by ^{1}H, ^{13}C, ^{31}P NMR, IR and HRMS (See Section 4.5).

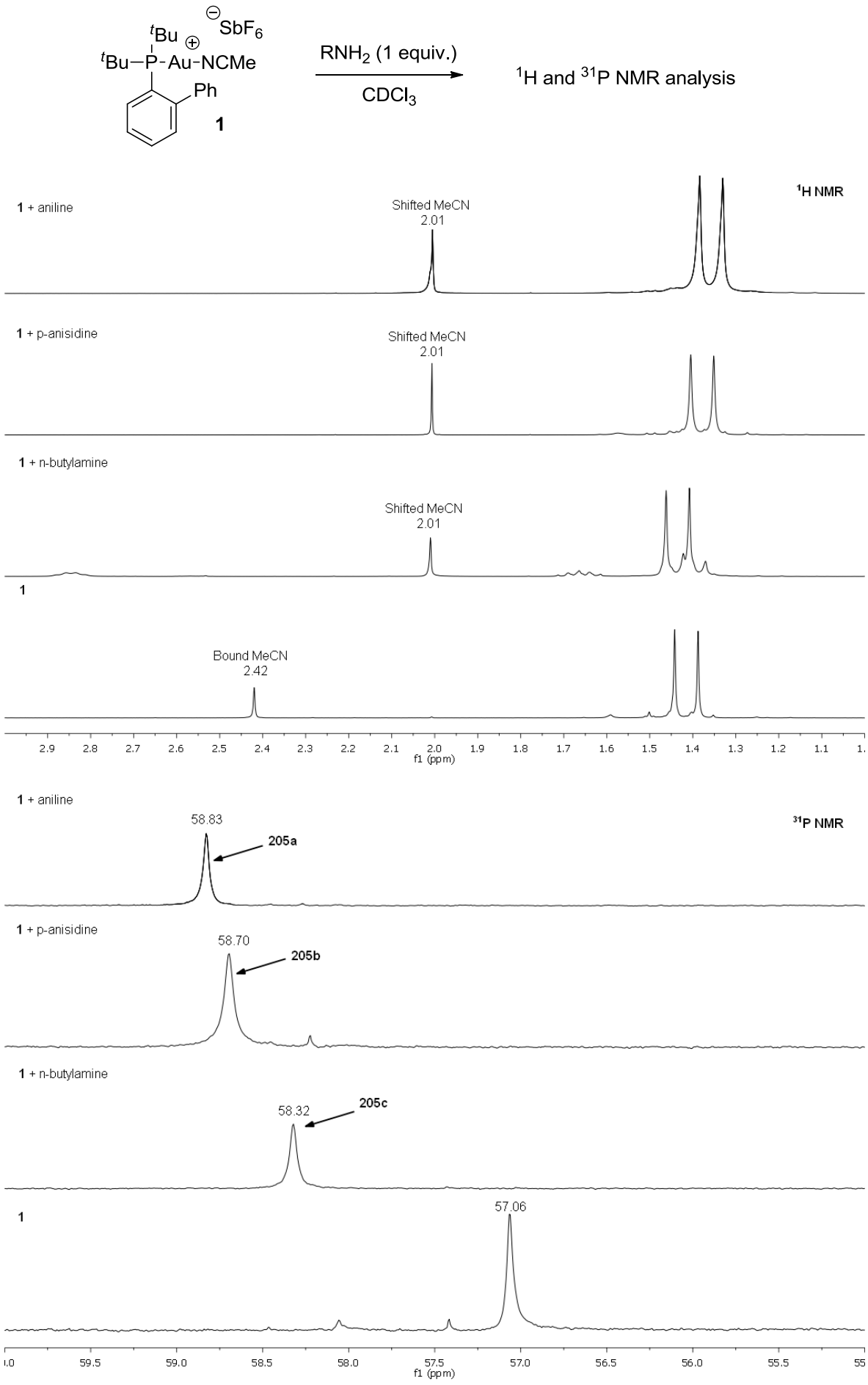
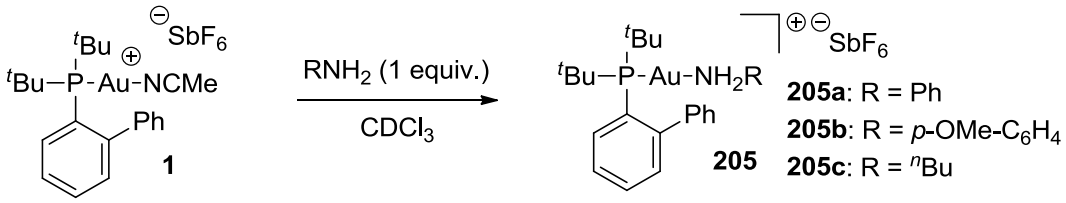


Figure 4.4. ^{1}H and ^{31}P NMR analysis of 1:1 *N*-nucleophile:**1**.

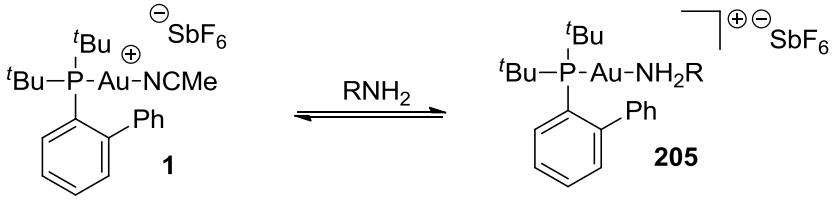


Scheme 4.18. Formation of monogold species with *N*-nucleophiles.

Analysis of the crystal structures suggested that there were no aurophilic interactions. Structures **205a**, **205b** and **205c** were found to have intermolecular Au-Au distances of 7.5686(4), 8.1290(3) and 7.6009(4) Å respectively, all of which are well out of the accepted range of aurophilic interactions (*ca.* 2.85-3.50 Å).[38] Similar to the digold structures **205a-c**, these amine-derived structures show a weak gold-arene interaction, possibly aiding the overall stabilisation of the complex. Structures **205a**, **205b** and **205c** showed Au-arene distances of 3.154, 3.162 and 3.172 Å respectively.

Our attempts to grow the corresponding NHC-versions and PPh_3-versions of these structures were unsuccessful, and led to decomposition. The failure to isolate these types of structures could be attributed to the resulting complexes not having the weak Au-arene interactions which occur in structures **205a**, **205b** and **205c**. Complex **205c** was found to remain stable in air for more than 6 months, demonstrating how the Au-arene interaction could be important to its stability.

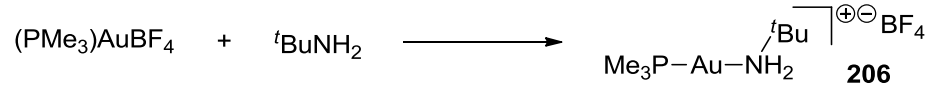
Interestingly, when less Lewis basic/nucleophilic amines were added to catalyst **1** (such as benzamide, $BocNH_2$ or $TsNH_2$), no reaction took place to form new complexes. The ^1H spectra of these mixtures showed that displacement of the MeCN ligand had not occurred, and the chemical shift of the phosphine ligand remained unchanged in the ^{31}P NMR spectra. Structures of the type **205** may still form on addition of these less nucleophilic amines, however the equilibrium may lie further toward catalyst **1** (Scheme 4.19).



Scheme 4.19. Formation of complex **205**.

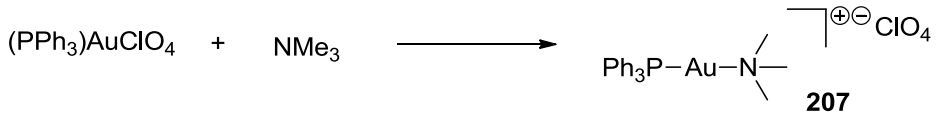
The less nucleophilic amines appearing unreactive with the parent catalyst **1** reflects nicely with the general reactivity observed in gold(I)-catalysis. Generally, less nucleophilic amines such as benzamide or *N*-protected amines are well tolerated in gold(I)-catalysed reactions, yielding the desired products. Conversely, *N*-nucleophiles which are seen to be more nucleophilic are less likely to react, resulting in either poor yields or failed reactions. The formation of complexes of the type **205** could be used as an explanation as to why reactions with these more nucleophilic amines are uncommon and low yielding. Presumably only substrates which are able to displace the amine from **205** will be reactive under gold(I) catalysis conditions.[4]

Similar structures have been prepared in an analogous procedure and reported in the literature. However, once again the catalytic abilities of these types of structures, and their role in catalytic cycles, have never been investigated.[41-43] For example, a report by Schmidbaur in 1995 demonstrated that *tert*-butylamine could be added to $(PMe_3)AuBF_4$ to form the monogold-amine complex **206** (Scheme 4.20).[41]

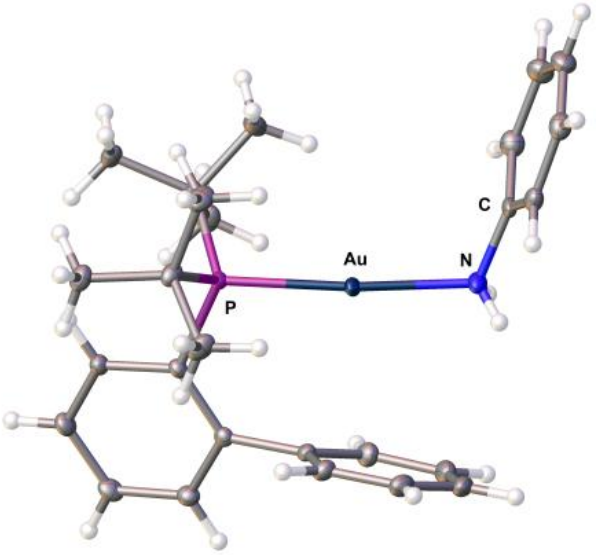


Scheme 4.20. Formation of complex **206** by Schmidbaur using *tert*-butylamine.

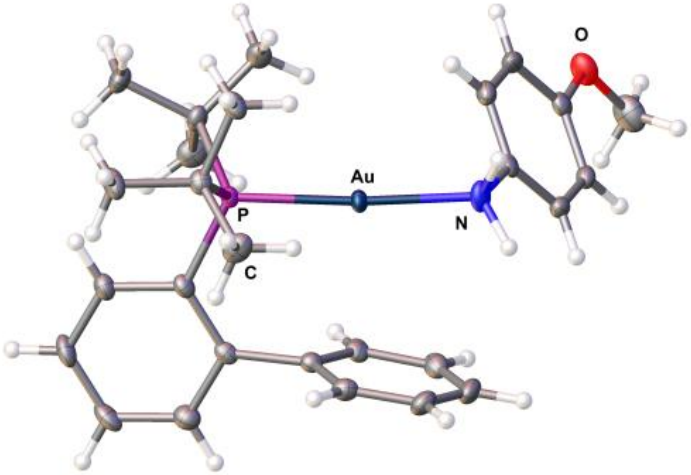
A tertiary amine was also shown to undergo the same reactivity with a gold(I) complex by Vicente in 1995 (Scheme 4.21), producing complex **207**.[43] With these two reported structures predating the rapid expansion of gold(I) catalysis, the catalytic abilities of the complexes were not investigated at the time.



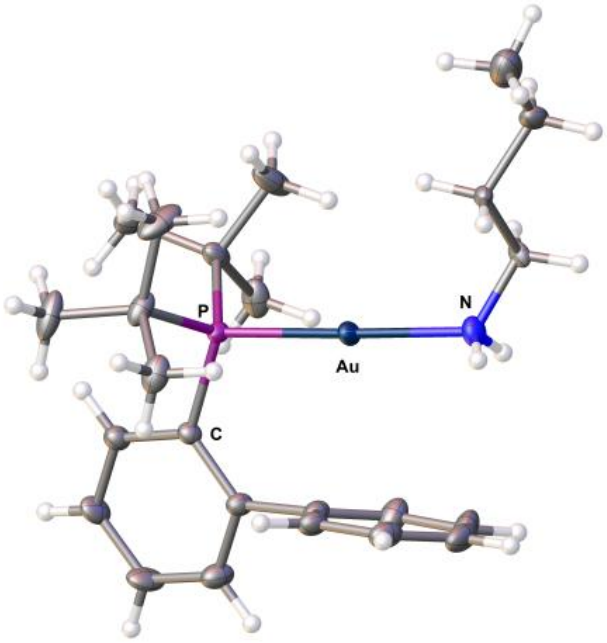
Scheme 4.21. Formation of **207** by Vicente using trimethylamine.



205a



205b



205c

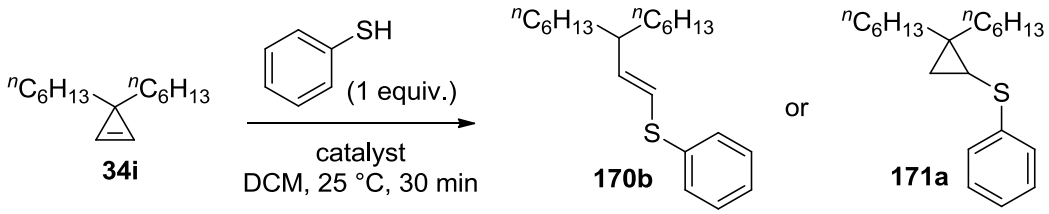
Figure 4.5. X-ray structures of **205a**, **205b** and **205c**. SbF_6^- counterion is omitted for clarity.

4.3.3 Catalytic Studies

Although similar complexes of type **174a-c** and **205a-c** are known in the literature, their catalytic abilities, as well as their possible formation during catalytic cycles, have never been probed. The related digold species with a bridging *carbon* species however, are known, and have been studied in terms of catalysis. These species were found to form in gold(I)-catalysed reactions, and form as a result of a competitive pathway at the protodeauration step of a mechanism (See section 4.1).[26, 28-32] Conversely, the digold species with bridging hydroxy ligand $[(Au(L)_2)(\mu\text{-OH})][X]$ has been found to be useful as active catalysts in reactions.[33, 34]

In order to determine catalytic ability, $[(Au(L)_2)(\mu\text{-SR})][X]$ **174a** was utilised as a catalyst in the nucleophilic addition of thiophenol to cyclopropene **34i** (Table 4.1). Under standard reaction conditions with **1**, vinylthioether **170b** is afforded as the sole product (entry 1). When complex **174a** was utilised as the catalyst in this reaction, product **170b** was obtained but in very low quantities (entry 3). Instead, the major product obtained was the cyclopropane product **171a**, which arises from the *uncatalysed* background addition reaction of thiophenol to cyclopropene **34i** (entry 2).

Table 4.1. Catalytic ability comparison of **1** and **174a**.



Entry	Catalyst	mol%	170b:171a[a]
1[b]	**1**	5	**170b** only
2	No catalyst	N/A	**171a** only
3	**174a**	2.5	1:20
4	**174a** + TfOH	2.5	2:1
5	TfOH	2.5	**171a** only

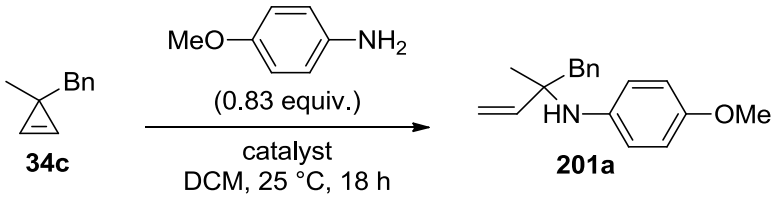
[a] Determined by ^{1}H NMR analysis of crude reaction mixture. [b] **1** is premixed with thiophenol in DCM before addition to **34i**.

This result using **174a** as a catalyst appears to show that this complex is the result of a deactivation pathway, and therefore not catalytically active. However, the experimental procedure dictates that thiophenol must be premixed with catalyst **1** in DCM *before* addition to cyclopropene **34i** (otherwise **171a** is formed as a side product), and it is known from the studies in 4.3.1 that complex **174a** will form immediately. This led us to consider the difference between using isolated complex **174a** as the catalyst, and when it would be formed *in situ* from **1** and thiophenol. The difference is the presence of H^+, liberated from thiophenol on the production of **174a** (see Scheme 4.16).

The proposed mechanism of formation of **174a-c** is considered to be reversible. If this is true addition of a source of H^+ could push the equilibrium back to parent catalyst **1** (Scheme 4.16). Thus the absence of H^+ when using isolated **174a** as the catalyst in this reaction means that the equilibrium lies firmly towards **174** and minimal **1** is released. Addition of TfOH to the reaction with **174a** significantly changes the reaction outcome, with the gold(I)-catalysed vinyl thioether product **170b** forming preferentially over the uncatalysed cyclopropane **171a** (entry 4). A control reaction was performed using TfOH as the only catalyst in the reaction, resulting in the formation of only cyclopropane **171a** (entry 5), hence demonstrating **170b** is formed *via* a gold(I)-catalysed pathway.

Next, we investigated the catalytic ability of complex **205**. The reaction of cyclopropenes and amines were found to result in poor conversion (maximum conversion = 42%). The low reactivity was attributed to the deactivation of gold(I) catalysts in the presence of amines. With the potential deactivated species [LAu-NH_2R][SbF_6] **205a-c** isolated and characterised, a study was carried out into their catalytic capability in the *p*-anisidine addition to cyclopropene **34c** (Table 4.2).

Table 4.2. Catalytic comparison of **1** and **205b**.



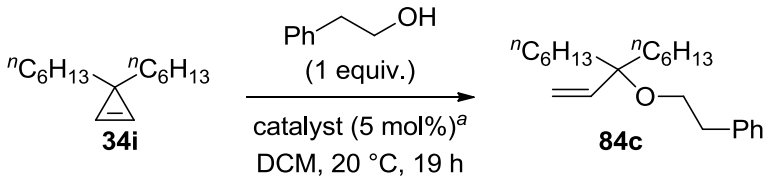
Entry	Catalyst	mol%	Conversion[a]
1	**1**	5	27%
2	**205b**	5	15%
3	**205b** + TfOH	5 + 5	13%

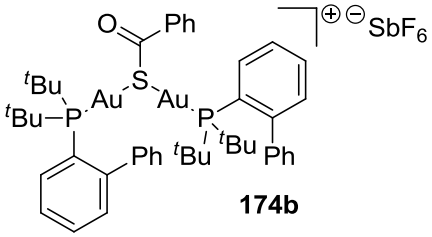
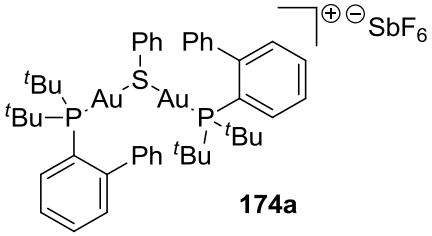
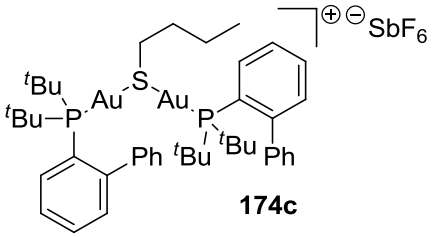
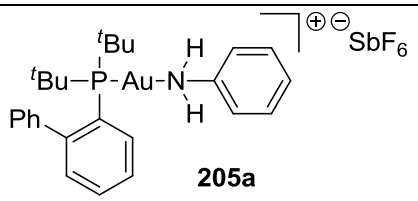
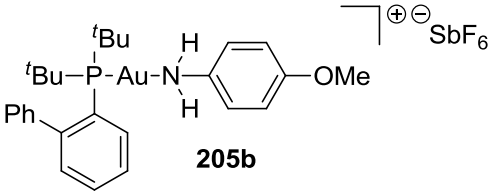
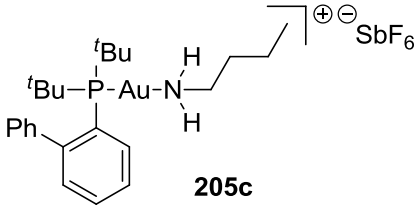
[a] Determined by analysis of ^{1}H NMR spectrum of crude reaction mixture.

A low 27% conversion to product was observed when catalyst **1** was used as the gold(I) catalysed in the reaction (entry 1). Conversion was further decreased to 15% on the addition of complex **205b** as the catalyst (entry 2). The addition of H^+ to the reaction showed no improvement on overall conversion to product (entry 3). This is expected upon consideration of the proposed mechanism of complex **205** formation, where the presence of H^+ does not alter the equilibrium between parent catalyst **1** and complex **205** (Scheme 4.19). From the results obtained from this short investigation, it is clear that structures of the type **205** are the likely cause of poor conversions in the gold(I)-catalysed amine additions to cyclopropenes.

In order to compare the catalytic abilities of structures **174a-c** and **205a-c**, the gold(I)-catalysed addition of alcohols to cyclopropenes was studied using the isolated complexes as the catalysts (Table 4.3). Previous work carried out in the Lee Group found that this reaction proceeds very well with a wide range of gold(I) catalysts to produce tertiary allylic ethers **84**.[44, 45]

Table 4.3. Comparison of catalytic ability of **174a-c** and **205a-c**.



Entry	Catalyst	Conversion[b]
1	 **174b**	47%
2	 **174a**	25%
3	 **174c**	<5%
4	 **205a**	47%
5	 **205b**	43%
6	 **205c**	34%

[a] 5 mol% with respect to gold, *i.e.* 2.5 mol% for digold species **174a-c**. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture.

Digold species with bridging thiolate **174a-c** were used as catalysts in the reaction and all resulted in poor conversion to expected product **84c** (entries 1-3), 47%, 25% and <5% for **174b**, **174a** and **21c** respectively. The trend reflects the Lewis basicity of the original RSH nucleophile used to make complex **174**, with the least nucleophilic thioacid (thiobenzoic acid) giving the highest conversion and the more nucleophilic alkyl thiol (*n*-butylmercaptan) showing just trace amount of product. The thiols with higher Lewis basicity will shift the equilibrium in Scheme 4.16 further toward the formation of **174**, and as a consequence results in less of the active catalyst **1** being available to perform the desired reaction.

A similar trend was observed when the amine-deactivated complexes **205a-c** were tested in the reaction (entries 4-6). The amines with an increased Lewis basicity resulted in lower conversions to the desired products; **205a**, **205b** and **205c** giving 47%, 43% and 34% respectively. Once again, the amines with higher Lewis basicity will push the equilibrium shown in Scheme 4.19 toward the formation of **205**, resulting in an overall decrease in concentration of the active parent catalyst **1**.

4.4 Conclusions & Future Work

On addition to gold(I) catalyst **1**, it was found that thiols react immediately to form digold species with bridging thiolate complexes $[(Au(L)_2)(\mu\text{-}SR)][SbF_6]$ **174**. Three of these complexes were isolated and fully characterised (**174a-c**), with the X-ray crystallography results showing evidence of aurophilic interactions between the two gold atoms within the complex, as well as a stabilising effect in the form of a weak gold-arene interaction.

The proposed pathway of formation of these complexes **174** is thought to be in equilibrium with the active parent catalyst **1** (Scheme 4.16). The presence of H^+ can alter the position of the equilibrium, allowing enough of catalyst **1** to reform and subsequently take part in gold(I)-catalysed reactions. If efforts are made to exclude H^+ from the equilibrium, the deactivated species **174** will be dominant, hence stagnating the gold(I)-catalysed reaction. The position of the equilibrium was also found to be affected by the Lewis basicity of the thiol nucleophile being used; those with a higher Lewis basicity (such as alkyl thiols) will result in the equilibrium shifting to form more of the deactivated complex **174**.

The addition of amines to gold(I) catalyst **1** showed a notably different outcome, resulting in the formation of monogold species $[LAu\text{-}NH_2R][SbF_6]$ **205**. Once again, three of these complexes were isolated and fully characterised (**205a-c**), with the X-ray crystallography results showing no intermolecular aurophilic interactions, however the weak stabilising effect of the gold-arene interaction was present as before. The digold species is not observed in any example, possibly due to the difference in acidity of the proton in **202** (Scheme 4.16) *vs.* **205** (Scheme 4.18).

In line with the thiol results, the Lewis basicity of the original amine in the complex determines the position of the equilibrium. Increasing the Lewis basicity of the amine results in an increased concentration of the deactivated complex **205**, which inhibits catalytic activity.

This study into catalyst deactivation provides an explanation into why *S*- and *N*-nucleophiles can severely dampen reactivity in gold(I)-catalysed reactions. The deactivated complexes **174a-c** and **205a-c** are all formed in competitive pathways with the desired reaction mechanism, therefore care should be employed when considering gold(I)-catalysed reactions that involve these potentially deactivating nucleophiles.

4.5 Experimental

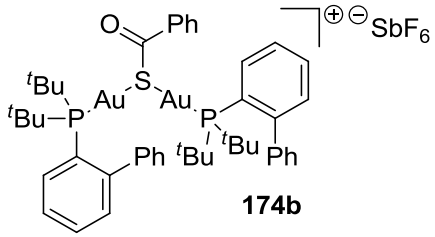
General Experimental Section

All reactions were carried out in air without the need for pre-dried solvents, in order to replicate the reaction conditions in gold(I) catalysed reactions, which are typically carried out in air. ^{1}H NMR spectra were recorded on Bruker AV 300 and AV 400 spectrometers at 300 and 400 MHz respectively and referenced to residual solvent. ^{13}C NMR spectra were recorded using the same spectrometers at 75 and 100 MHz respectively. Chemical shifts (δ in ppm) were referenced to tetramethylsilane (TMS) or to residual solvent peaks ($CDCl_3$ at δ 7.26). For ^{31}P NMR, chemical shifts were referenced against H_3PO_4 at δ 0 ppm. *J* values are given in Hz and s, d, dd, t, q and m abbreviations correspond to singlet, doublet, doublet of doublet, triplet, quartet and multiplet. Mass spectrometry data was acquired at the EPSRC UK National Mass Spectrometry Facility at Swansea University. Infrared spectra were obtained on Perkin-Elmer Spectrum 100 FT-IR Universal ATR Sampling Accessory, deposited neat or as a chloroform solution to a diamond/ZnSe plate. Elemental analyses were determined by the departmental service (HWU). Flash column chromatography was carried out using Matrix silica gel 60 from Fisher Chemicals and TLC was performed using Merck silica gel 60 F254 precoated sheets and visualised by UV (254 nm) or stained by the use of aqueous acidic ceric ammonium molybdate. Petrol ether refers to petroleum ether (40 – 60 °C). Dichloromethane (DCM) was purchased from Fisher and used without further purification. All nucleophiles were purchased from Sigma-Aldrich or Acros, and used without further purification.

General Experimental Procedure for Crystals 174a-c and 205a-c.

Catalyst **1** and the nucleophile RSH or RNH_2 (1 equiv.) were added to an NMR tube, and dissolved in $CDCl_3$ (0.75 mL). ^{1}H and ^{31}P NMR were obtained from the resulting crude mixture. The solution was then decanted into a vial, and crystals were grown by vapour diffusion from $CDCl_3$/hexane. The crystals were washed with hexane and dried under reduced pressure.

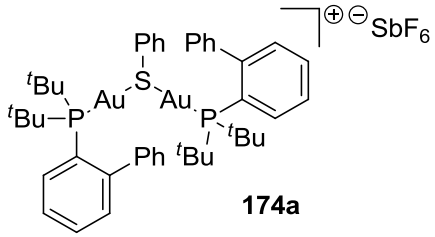
Compound 174b



174b

Complex **174b** was obtained as yellow crystals (9.3 mg, 0.0068 mmol, 26%). M.p. 195 °C (decomposes); ν_{max}/cm^{-1} 3056 w, 2955 m, 2853 w, 1673 m, 1615 w, 1602 w, 1472 m; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 – 7.80 (m, 4H, Ar-H), 7.64 – 7.11 (m, 19H, Ar-H), 1.30 (d, *J* (^{1}H-^{31}P) = 16.0 Hz, 36H, C(C*H*$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.5 (C), 149.2 (d, *J* (^{13}C–^{31}P) = 13.5 Hz, C), 143.1 (d, *J* (^{13}C–^{31}P) = 6.8 Hz, C), 138.3 (C), 134.5 (d, *J* (^{13}C–^{31}P) = 11.8 Hz, CH), 133.9 (CH), 133.3 (CH) (d, *J* (^{13}C–^{31}P) = 7.7 Hz, CH), 131.4 (CH), 129.7 (CH), 129.4 (CH), 129.1 (d, *J* (^{13}C–^{31}P) = 16.1 Hz, CH), 128.9 (CH), 128.7 (CH), 128.3 (CH), 128.0 (CH), 127.8 (d, *J* (^{13}C–^{31}P) = 7.0 Hz, CH), 125.4 (d, *J* (^{13}C–^{31}P) = 45.0 Hz, C), 38.2 (d, *J* (^{13}C–^{31}P) = 23.8 Hz, C), 30.8 (d, *J* (^{13}C–^{31}P) = 6.7 Hz, CH_3). ^{31}P NMR (121 MHz, $CDCl_3$) δ 63.65. Found (NESI) $[M\text{-}SbF_6]^+$ 1127.3084, $C_{47}H_{59}Au_2OP_2S$ requires 1127.3087.

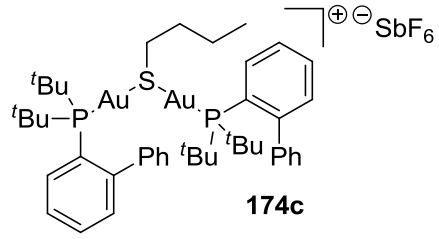
Compound 174a



174a

Complex **174a** was obtained as white crystals (8.4 mg, 0.0065 mmol, 97%). M.p. 184 °C (decomposes); ν_{max}/cm^{-1} 2951 m, 2886 w, 1577 m, 1469 m, 1440 m; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.93 – 7.84 (m, 2H, Ar-H), 7.62 – 7.45 (m, 6H, Ar-H), 7.35 – 7.16 (m, 11H, Ar-H), 7.15 – 7.09 (m, 4H, Ar-H), 1.37 (d, *J* (^{1}H–^{31}P) = 15.8 Hz, 36H, C(C*H*$_3$)$_3$). ^{13}C NMR (75 MHz, CD_2Cl_2) δ 149.8 (d, *J* (^{13}C–^{31}P) = 14.2 Hz, C), 143.3 (d, *J* (^{13}C–^{31}P) = 6.7 Hz, C), 134.4 (CH), 133.73 (d, *J* (^{13}C–^{31}P) = 7.6 Hz, CH), 133.72 (CH), 131.7 (CH), 129.9 (CH), 129.7 (CH), 129.3 (CH), 129.2 (CH), 128.5 (CH), 128.1 (CH), 128.0 (CH), 127.8 (C), 127.5 (CH), 125.8 (d, *J* (^{13}C–^{31}P) = 44.3 Hz, C), 38.5 (d, *J* (^{13}C–^{31}P) = 23.7 Hz, C), 31.3 (d, *J* (^{13}C–^{31}P) = 6.9 Hz, CH_3). ^{31}P NMR (121 MHz, CD_2Cl_2) δ 62.87. Found (NESI) [*M*-SbF_6]$^{+}$ 1099.3137, $C_{46}H_{59}Au_2OP_2S$ requires 1099.3138.

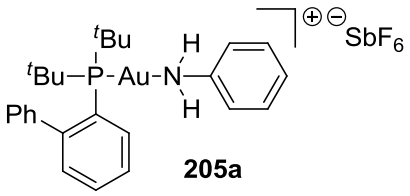
Compound 174c



174c

Complex **174c** was obtained as yellow crystals (19.3 mg, 0.015 mmol, 55%). M.p. 193 °C; ν_{max}/cm^{-1} 2956 m, 2901 w, 2872 w, 1462 m, 1441 m, 1430 m; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 – 7.83 (m, 2H, Ar-H), 7.61 – 7.09 (m, 16H, Ar-H), 2.65 – 2.50 (m, 2H, SC*H*$_2$), 1.56 – 1.25 (m, 4H, alkyl CH_2), 1.40 (d, *J* (^{1}H–^{31}P) = 15.7 Hz, 36H, C(C*H*$_3$)$_3$), 0.84 (t, *J* = 7.3 Hz, 3H, CH_2C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3 (d, *J* (^{13}C–^{31}P) = 14.2 Hz, C), 143.1 (d, *J* (^{13}C–^{31}P) = 6.7 Hz, C), 134.1 (CH), 133.3 (d, *J* (^{13}C–^{31}P) = 7.8 Hz, CH), 131.2 (CH), 129.6 (CH), 128.7 (CH), 128.0 (CH), 127.6 (d, *J* (^{13}C–^{31}P) = 6.9 Hz, CH), 125.8 (d, *J* (^{13}C–^{31}P) = 43.3 Hz, C), 40.1 (CH_2), 38.2 (d, *J* (^{13}C–^{31}P) = 23.5 Hz, C), 32.9 (CH_2), 31.0 (d, *J* (^{13}C–^{31}P) = 6.8 Hz, CH_3), 22.0 (CH_2), 13.9 (CH_3). ^{31}P NMR (162 MHz, $CDCl_3$) δ 62.75. Found (NESI) [*M*-SbF_6]$^{+}$ 1079.3434, $C_{44}H_{63}Au_2OP_2S$ requires 1079.3451

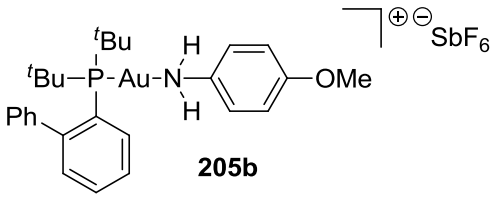
Compound 205a



205a

Complex **205a** was obtained as white crystals (21.0 mg, 0.025 mmol, 98%). M.p. 185 °C (decomposes); ν_{max}/cm^{-1} 3314 w, 3266 m, 3016 w, 2954 w, 1605 m, 1590 m, 1496 m, 1474 m, 1462 m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (td, *J* = 7.9 Hz, 1.8, 1H, Ar-H), 7.65 – 7.51 (m, 5H, Ar-H), 7.34 – 7.24 (m, 5H, Ar-H), 7.20 – 7.12 (m, 1H, Ar-H), 7.01 (d, *J* = 7.6 Hz, 2H, Ar-H), 4.67 (br. s, 2H, N*H*$_2$), 1.36 (d, *J* (^{1}H–^{31}P) = 16.1 Hz, 18H, C(C*H*$_3$)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1 (d, *J* (^{13}C–^{31}P) = 12.1 Hz, C), 144.0 (d, *J* (^{13}C–^{31}P) = 6.3 Hz, C), 133.4 (CH), 133.3 (d, *J* (^{13}C–^{31}P) = 10.1 Hz, CH), 131.5 (d, *J* (^{13}C–^{31}P) = 2.1 Hz, CH), 130.5 (CH), 129.8 (CH), 129.2 (CH), 127.6 (d, *J* (^{13}C–^{31}P) = 7.3 Hz, CH), 127.2 (CH), 126.3 (broad, C), 125.1 (d, *J* (^{13}C–^{31}P) = 48.5 Hz, C), 121.7 (broad, CH), 38.0 (d, *J* (^{13}C–^{31}P) = 26.2 Hz, C), 30.9 (d, *J* (^{13}C–^{31}P) = 6.1 Hz, CH_3). ^{31}P NMR (162 MHz, $CDCl_3$) δ 58.86. Found (NESI) [*M*-SbF_6]$^{+}$ 588.2089, $C_{26}H_{34}AuNP$ requires 588.2089. Anal. Calc. for $C_{26}H_{34}AuF_6NPSb$: C, 37.88; H, 4.17; N, 1.70. Found: C, 37.88; H, 4.13; N, 1.34.

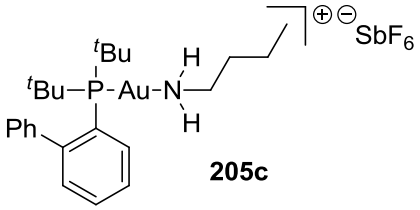
Compound 205b



205b

Complex **205b** was obtained as white crystals (22.1 mg, 0.026 mmol, 99%). M.p. 173 °C (decomposes); ν_{max}/cm^{-1} 3312 w, 3268 w, 2960 w, 1607 w, 1577 m, 1510 s, 1458 m, 1245 s; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 – 7.81 (m, 1H, Ar-H), 7.63 – 7.50 (m, 4H, Ar-H), 7.36 – 7.22 (m, 4H, Ar-H), 6.96 (d, *J* = 8.9 Hz, 2H, Ar-H), 6.80 (d, *J* = 8.9 Hz, 2H, Ar-H), 4.57 (br s, 2H, N*H*$_2$), 3.78 (s, 3H, OC*H*$_3$), 1.38 (d, *J* (^{1}H–^{31}P) = 16.1 Hz, 18H, C(C*H*$_3$)$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7 (broad, C), 149.2 (d, *J* (^{13}C–^{31}P) = 12.5 Hz, C), 144.0 (d, *J* (^{13}C–^{31}P) = 6.5 Hz,), 133.4 (d, *J* (^{13}C–^{31}P) = 6.0 Hz, CH), 133.3 (d, *J* (^{13}C–^{31}P) = 10.3 Hz, CH), 131.4 (d, *J* (^{13}C–^{31}P) = 2.2 Hz, CH), 130.5 (CH), 129.2 (CH), 127.6 (d, *J* (^{13}C–^{31}P) = 7.4 Hz, CH), 127.2 (CH), 125.1 (d, *J* (^{13}C–^{31}P) = 48.4 Hz, C), 123.1 (broad, C), 114.9 (CH), 114.9 (CH), 55.7 (CH_3), 38.0 (d, *J* (^{13}C–^{31}P) = 26.3 Hz, C), 30.9 (d, *J* (^{13}C–^{31}P) = 6.1 Hz, CH_3). ^{31}P NMR (121 MHz, $CDCl_3$) δ 58.71. Found (NESI) [*M*-SbF_6]$^{+}$ 618.2182, $C_{27}H_{36}AuNOP$ requires 618.2195. Anal. Calc. for $C_{27}H_{36}AuF_6NOPSb$: C, 37.96; H, 4.26; N, 1.64. Found: C, 37.76; H, 4.25; N, 1.52.

Compound 205c



205c

Complex **205c** was obtained as white crystals (19.7 mg, 0.024 mmol, 94%). M.p. 173 °C (decomposes); ν_{max}/cm^{-1} 3320 m, 3276 m, 2962 m, 2902 w, 1474 s, 1461 s; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (td, *J* = 7.6, 1.7 Hz, 1H, Ar-H), 7.64 – 7.47 (m, 4H, Ar-H), 7.35 – 7.17 (m, 4H, Ar-H), 2.91 – 2.68 (m, 4H, N*H*$_2$C*H*$_2$), 1.54 – 1.23 (m, 22H, C(C*H*$_3$)$_3$ & C*H*$_2$C*H*$_2$CH$_3$), 0.90 (t, *J* = 7.3 Hz, 3H, CH$_2$C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2 (d, *J* ($^{13}C–^{31}P$) = 12.7 Hz, C), 143.8 (d, *J* ($^{13}C–^{31}P$) = 6.6 Hz, C), 133.6 (d, *J* ($^{13}C–^{31}P$) = 3.2 Hz, CH), 133.3 (d, *J* ($^{13}C–^{31}P$) = 7.5 Hz, CH), 131.4 (d, *J* ($^{13}C–^{31}P$) = 2.1 Hz, CH), 130.3 (CH), 128.9 (CH), 127.6 (d, *J* ($^{13}C–^{31}P$) = 7.3 Hz, CH), 127.4 (CH), 125.3 (d, *J* ($^{13}C–^{31}P$) = 47.8 Hz, C), 45.5 (CH_2), 38.0 (d, *J* ($^{13}C–^{31}P$) = 26.3 Hz, C), 34.2 (CH_2), 30.9 (d, *J* ($^{13}C–^{31}P$) = 6.1 Hz, CH_3), 19.7 (CH_2), 13.8 (CH_3). ^{31}P NMR (121 MHz, $CDCl_3$) δ 58.30; Found (NESI) [*M*-SbF_6]$^+$ 568.2399, $C_{24}H_{38}AuNP$ requires 568.2402. Anal. Calc. for $C_{24}H_{38}AuF_6NPSb$: C, 35.84; H, 4.77; N, 1.74. Found: C, 36.13; H, 4.75; N, 1.49.

Crystal data.

Single crystal X-ray diffraction data were collected on crystals **174b**, **174c**, **205a-c** which were coated in Paratone-N oil and mounted on an X8 Apex2 diffractometer with a MiTiGen Micromount. Diffraction data were collected at 100 K with graphite monochromated MoKα radiation from a sealed X-ray tube set at 50 kV and 35 mA. Diffraction data for **174a** were collected on an Agilent SuperNova, Dual, Atlas diffractometer using Cu Kα radiation (1.5418 Å) with mirror optics. The crystal was kept at 120.01(10) K during data collection. Using Olex2,[46] the structure was solved with the XS[47] structure solution program using Direct Methods and refined with the XL[47] refinement package using Least Squares minimisation. All non hydrogen atoms were refined anisotropically. All H atoms including water were constrained to idealised geometries apart from N bound H atoms in **205a-c**. CCDC-914704 (**174b**), -896069 (**174a**), -914705 (**174c**), -914706 (**205a**), -914707 (**205b**), and -914708 (**205c**), contain the supplementary crystallographic data for this paper (See Tables 4.4 & 4.5 for crystal data and structure refinements).

Table 4.4. Crystal data and structure refinements for **174a-c**.

	174b	**174a**	**174c**
Empirical formula	$C_{47}H_{59}OF_6P_2SSbAu_2$	$C_{46}H_{59}Au_2F_6P_2SSb$	$C_{44}H_{63}Au_2F_6P_2SSb.0.5(CHCl_3)$
Formula weight	1363.63	1335.61	1375.31
Temperature/K	100(2)	120.01(10)	100.15
Crystal system	triclinic	monoclinic	monoclinic
Space group	P-1	Cc	$P2_1/n$
a/Å	13.4006(7)	24.6918(3)	12.0540(8)
b/Å	13.5192(7)	13.08924(15)	30.084(2)
c/Å	15.7860(8)	29.3558(4)	13.5903(8)
α/°	68.403(2)	90.0	90.00
β/°	80.115(2)	90.7654(11)	96.316(3)
γ/°	65.851(2)	90.0	90.00
Volume/Å^3	2425.6(2)	9486.84(19)	4898.4(5)
Z	2	8	4
ρ_{calc}mg/mm^3	1.867	1.870	1.865
m/mm^{-1}	6.752	17.388	6.765
F(000)	1316.0	5152.0	2660.0
Crystal size/mm^3	0.40 × 0.40 × 0.30	0.2426 × 0.123 × 0.056	0.38 × 0.32 × 0.28
2Θ range for data collection	2.78 to 52.74°	6.017 to 152.5034°	2.7 to 66.64°
Index ranges	$-16 \le h \le 16$, $-13 \le k \le 16$, $-18 \le l \le 19$	$-31 \le h \le 29$, $-16 \le k \le 15$, $-36 \le l \le 36$	$-18 \le h \le 18$, $-46 \le k \le 46$, $-20 \le l \le 20$
Reflections collected	35962	77919	136649
Independent reflections	9865[R(int) = 0.0351]	19283[R(int) = 0.0447]	18698[R(int) = 0.0549]
Data/restraints/parameters	9865/0/553	19283/2/1069	18698/13/600
Goodness-of-fit on F^2	1.139	1.041	1.013
Final R indexes [I>=2σ(I)]	R_1 = 0.0216, wR_2 = 0.0545	R_1 = 0.0313, wR_2 = 0.0819	R_1 = 0.0341, wR_2 = 0.0768
Final R indexes [all data]	R_1 = 0.0259, wR_2 = 0.0707	R_1 = 0.0315, wR_2 = 0.0820	R_1 = 0.0479, wR_2 = 0.0825
Largest diff. peak/hole / e Å^{-3}	0.99/-1.48	1.53/-0.91	4.08/-4.73

Table 4.5. Crystal data and structure refinements for **205a-c**.

	205a	**205b**	**205c**
Empirical formula	$C_{26}H_{34}NF_6PSbAu$	$C_{27}H_{36}AuF_6NOPSb$	$C_{24}H_{38}AuF_6NPSb$
Formula weight	824.23	854.25	804.24
Temperature/K	100.15	100(2)	100(2)
Crystal system	monoclinic	monoclinic	monoclinic
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$
a/Å	7.5686(4)	13.1268(4)	7.6009(4)
b/Å	17.4546(9)	11.7372(4)	17.7750(9)
c/Å	20.8291(11)	19.9682(7)	20.5702(10)
α/°	90.00	90.00	90.00
β/°	95.628(3)	106.108(2)	98.499(2)
γ/°	90.00	90.00	90.00
Volume/$Å^3$	2738.4(2)	2955.75(17)	2748.6(2)
Z	4	4	4
$\rho_{calc}mg/mm^3$	1.999	1.920	1.943
m/mm^{-1}	6.453	5.985	6.426
F(000)	1584.0	1648.0	1552.0
Crystal size/mm^3	0.43 × 0.38 × 0.26	0.22 × 0.12 × 0.08	0.4 × 0.38 × 0.04
2Θ range for data collection	4.58 to 72.04°	4.82 to 60.32°	3.04 to 70.38°
Index ranges	$-12 \le h \le 12$, $-28 \le k \le 28$, $-32 \le l \le 34$	$-18 \le h \le 17$, $0 \le k \le 16$, $0 \le l \le 28$	$-12 \le h \le 12$, $-27 \le k \le 28$, $-33 \le l \le 29$
Reflections collected	69144	102285	82430
Independent reflections	12891[R(int) = 0.0376]	8722[R(int) = 0.0691]	11854[R(int) = 0.0375]
Data/restraints/parameters	12891/0/337	8722/2/359	11854/6/349
Goodness-of-fit on F^2	1.024	1.029	1.026
Final R indexes [I>=2σ (I)]	$R_1 = 0.0235$, $wR_2 = 0.0458$	$R_1 = 0.0294$, $wR_2 = 0.0508$	$R_1 = 0.0285$, $wR_2 = 0.0639$
Final R indexes [all data]	$R_1 = 0.0324$, $wR_2 = 0.0480$	$R_1 = 0.0436$, $wR_2 = 0.0546$	$R_1 = 0.0466$, $wR_2 = 0.0691$
Largest diff. peak/hole / e $Å^{-3}$	3.29/-2.04	0.72/-1.03	1.76/-1.80

General Procedure for Table 4.1

A solution of thiophenol (1 equiv.) and catalyst (2.5 mol%) in DCM (0.2 mL) was added to a solution of cyclopropene **34i** (1 equiv.) in DCM (0.52 mL) at 25 °C and stirred for 30 min. The solution was then filtered through a plug of silica with diethyl ether, and concentrated under reduced pressure. The reaction mixture was analysed by ^{1}H NMR in $CDCl_3$ to determine **170b**:**171a** ratio by comparison with literature known spectra.[36]

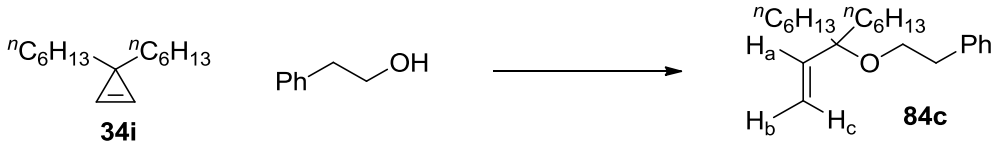
General Procedure for Table 4.2

Catalyst (5 mol%) was added to a stirred solution of cyclopropene **34c** (1.2 equiv.) and *p*-anisidine (1 equiv.) in DCM (0.1 M). The resulting solution was stirred for 18 h at 25 °C, filtered through a silica plug with ether and concentrated under reduced pressure. The reaction mixture was then analysed by ^{1}H NMR in $CDCl_3$ to determine reaction conversion by comparison with literature known spectra.[36]

General Procedure for Table 4.3

Catalyst (5 mol% with respect to gold) was added in one portion to a stirred solution of cyclopropene **34i** (1 equiv.) and phenethyl alcohol (1 equiv.) in DCM (0.48 M). The resulting solution was stirred for 19 h at 20 °C, the mixture was then filtered through a silica plug with ether and concentrated under reduced pressure. The reaction mixture was then analysed by ^{1}H NMR in $CDCl_3$ to determine reaction conversion by comparison with spectra of isolated **84c**.

(2-((7-Vinyltridecan-7-yl)oxy)ethyl)benzene **84c:**



3,3-Dihexylcycloprop-1-ene **34i** (14.8 mg, 0.071 mmol) was dissolved in DCM (0.15 mL) and phenethyl alcohol (52 μL, 52.8 mg, 0.432 mmol) was added *via* Hamilton syringe. Catalyst **1** (2.7 mg, 0.0035 mmol) was added, and the solution was allowed to stir for 15 minutes at 20 °C. The reaction mixture was then filtered through a silica plug (40:1 petroleum ether:diethyl ether) and concentrated under reduced pressure. ^{1}H NMR analysis on the crude mixture showed that the tertiary allylic ether was the only product. The product was purified using flash column chromatography (neat petroleum ether → 40:1 petroleum ether:diethyl ether). The desired product **84c** was obtained as a colourless oil (19.9 mg, 0.060 mmol, 85%).

ν_{max}/cm^{-1} 2929 s 2857 m (C-H), 1639 w (C=C), 1605 w 1496 m 1455 m (aromatic C=C), 1078 s (C-O-C);^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.15 (m, 5H, Ar-H), 5.62 (dd, *J* = 17.6 Hz, 11.1, 1H, H_a), 5.13 (dd, *J* = 11.1, 1.6 Hz, 1H, H_b), 5.07 (dd, *J* = 17.6, 1.6 Hz, 1H, H_c), 3.43 (t, *J* = 7.3 Hz, 2H, $OC\underline{H_2}CH_2$), 2.83 (t, *J* = 7.3 Hz, 2H, $CH_2C\underline{H_2}Ph$), 1.54 – 1.09 (m, 20H, alkyl CH_2), 0.88 (t, *J* = 6.7 Hz, 6H, $CH_2C\underline{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 143.1 (CH), 139.7 (C), 129.2 (CH), 128.3 (CH), 126.2 (CH), 114.7 (CH_2), 79.4 (C), 62.9 (CH_2), 37.4 (CH_2), 35.4 (CH_2), 32.0 (CH_2), 30.0 (CH_2), 23.1 (CH_2), 22.8 (CH_2), 14.3 (overlapping CH_3). Found (APCI) $[M+NH_4]^+$ 348.3259, $C_{23}H_{42}ON$ requires 348.3261.

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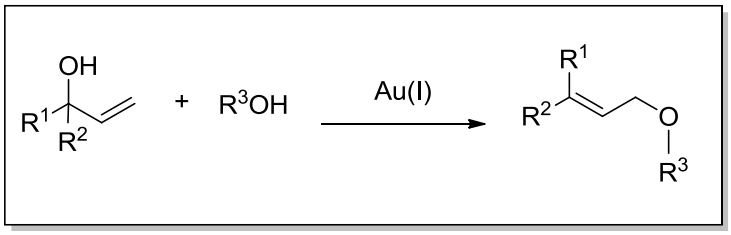
Chapter 5 – Gold(I)-Catalysed Reactions with Allylic Alcohols

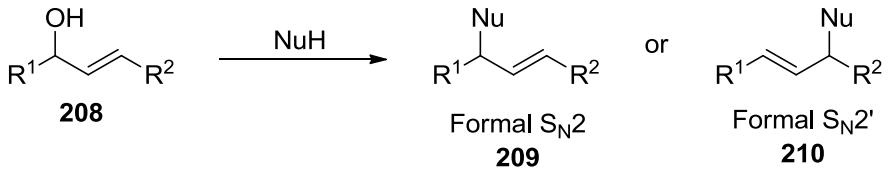


Acknowledgements: The author thanks Nina Schopf (Erasmus exchange student) for her input into this chapter (Section 5.3.1, Table 5.7, entry 5. Table 5.8, entries 13 & 14). Allylic alcohol starting materials were prepared by various members of the Lee Group (**235a**, **235b** & **235h** by Ben Dickson. **235j** & **235k** by Mark Lauchlan. **235l** & **235m** by Nina Schopf). The work reported in Section 5.3.2 was carried out with Eloi Coutant (Erasmus exchange student), where this is so, his contribution is acknowledged in the text. Section 5.3.3 was completed in collaboration with the Crowley Group from the University of Otago; the author thanks James Wright for the synthesis of all (Trz)-gold(I) complexes (**7**-**12**).

5.1 Introduction

Although the chemistry of cyclopropenes is extremely interesting from an academic point of view, there are some limitations that restrict it being adopted by the wider chemical community. Although we routinely synthesise cyclopropenes on gram scale, there are limited methods for synthesising cyclopropenes on larger scale, and their high ring strain dictates that there can be potential stability issues. For novel reactions to be embraced by industry, the reactions must be high yielding and relatively inexpensive. Thus, there is constant pressure on researchers to develop new reactions which require little modification to the starting materials, and to have reasonably mild reaction conditions.

Allylic alcohols have become increasingly utilised in organic synthesis as building blocks to much more complex structures. As starting materials, they are highly desired due to their vast availability through commercial sources, or from well-known and reliable reactions; such as vinyl Grignard additions to aldehydes and ketones. Allylic alcohols have the ability to react *via* formal S_N2 or S_N2' regioselectivities; hence leading the way to vast libraries of products (Scheme 5.1).



Scheme 5.1. Potential reactivity of allylic alcohols with nucleophiles.

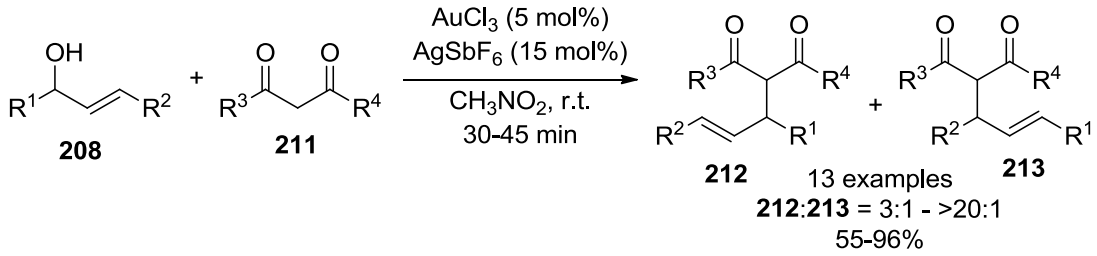
These reactions have been shown to proceed using transition metal catalysis, with both intra- and intermolecular examples prevalent in the literature.[1-3] There have been examples of carbon-carbon bond formation, as well as carbon-heteroatom formation.

5.1.1 Gold & Allylic Alcohols

Gold(I) catalysis, as stated previously, is well known for its activation of alkynes and allenes toward nucleophilic attack.[4-11] However, there is less precedent for their use with alkenes. These reactions tend to require higher temperatures, and reaction times are usually longer. The possibility of utilising gold catalysis with alkenes is significantly increased when a potential leaving group is introduced to the substrate. Consequently, allylic alcohols and their activated derivatives have been used as suitable substrates for gold-catalysed reactions.

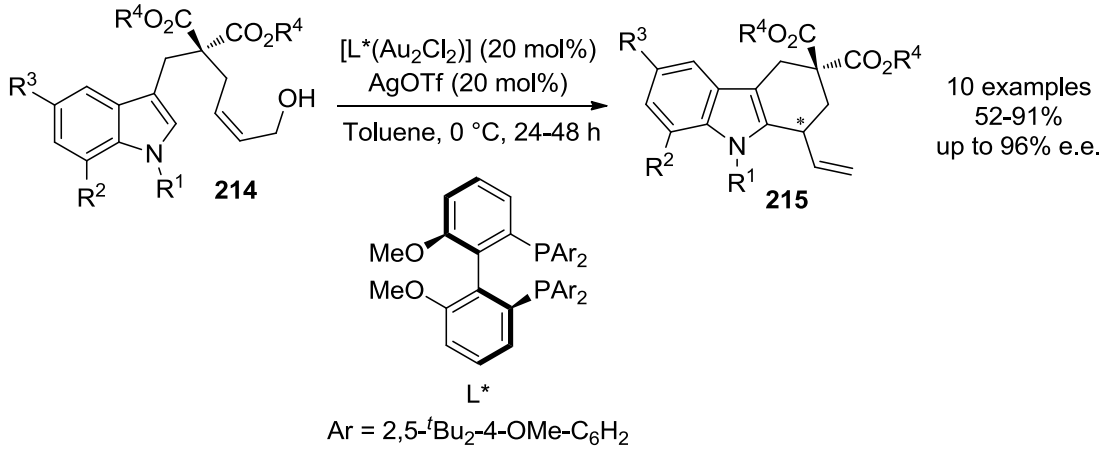
Both gold(I) and gold(III) have been used to catalyse a wide range of transformations from allylic alcohol substrates. Gold(III) tends to activate preferentially at the oxygen, explained by its increased oxophilicity in comparison to gold(I); which is selectively more carbophilic.[12, 13] Using gold(III) as a catalyst leads to potential issues with the mechanism as there are two possible outcomes: formal S_N2 or S_N2' products. The higher oxophilicity of gold(III) can lead to allylic cations being formed in the reaction, especially if there is access to conjugation. Control over regioselectivity can decrease because of this.

This is highlighted in the reaction described by Chan, in which allylic alcohols **208** are reacted with 1,3-diketones **211**, catalysed by gold(III) (Scheme 5.2).[14] Excellent yields are achieved, but mixtures of regioisomers are observed with a number of substrates; with the major always being the formal S_N2 product. It was noted that when R^1 and R^2 are differing substituents, the **212**:**213** regioselectivity drops to as low as 3:1.



Scheme 5.2. Gold(III)-catalysed allylic alkylation by Chan.

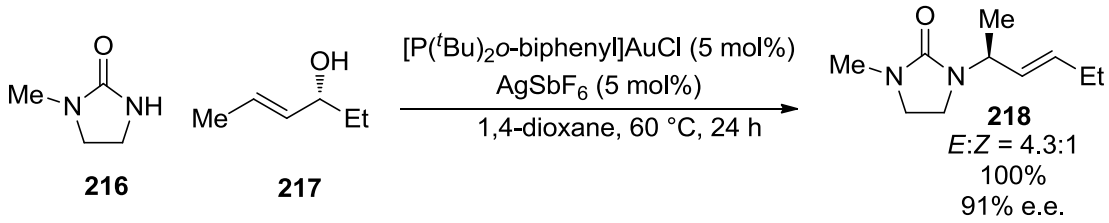
Bandini and co-workers extended the field of gold-catalysed allylic alkylations with an intramolecular reaction of indole substrates **214** (Scheme 5.3).[15, 16] The method elegantly highlights the use of chiral gold(I)-catalysts to activate allylic alcohols, forming functionalised tetrahydrocarbazoles **215**. The authors state that rigorous water exclusion is required to obtain good yields. Methyl substitution at R^1 is not tolerated, presumably due to unfavourable steric interactions at the cyclisation site at the C2-position.



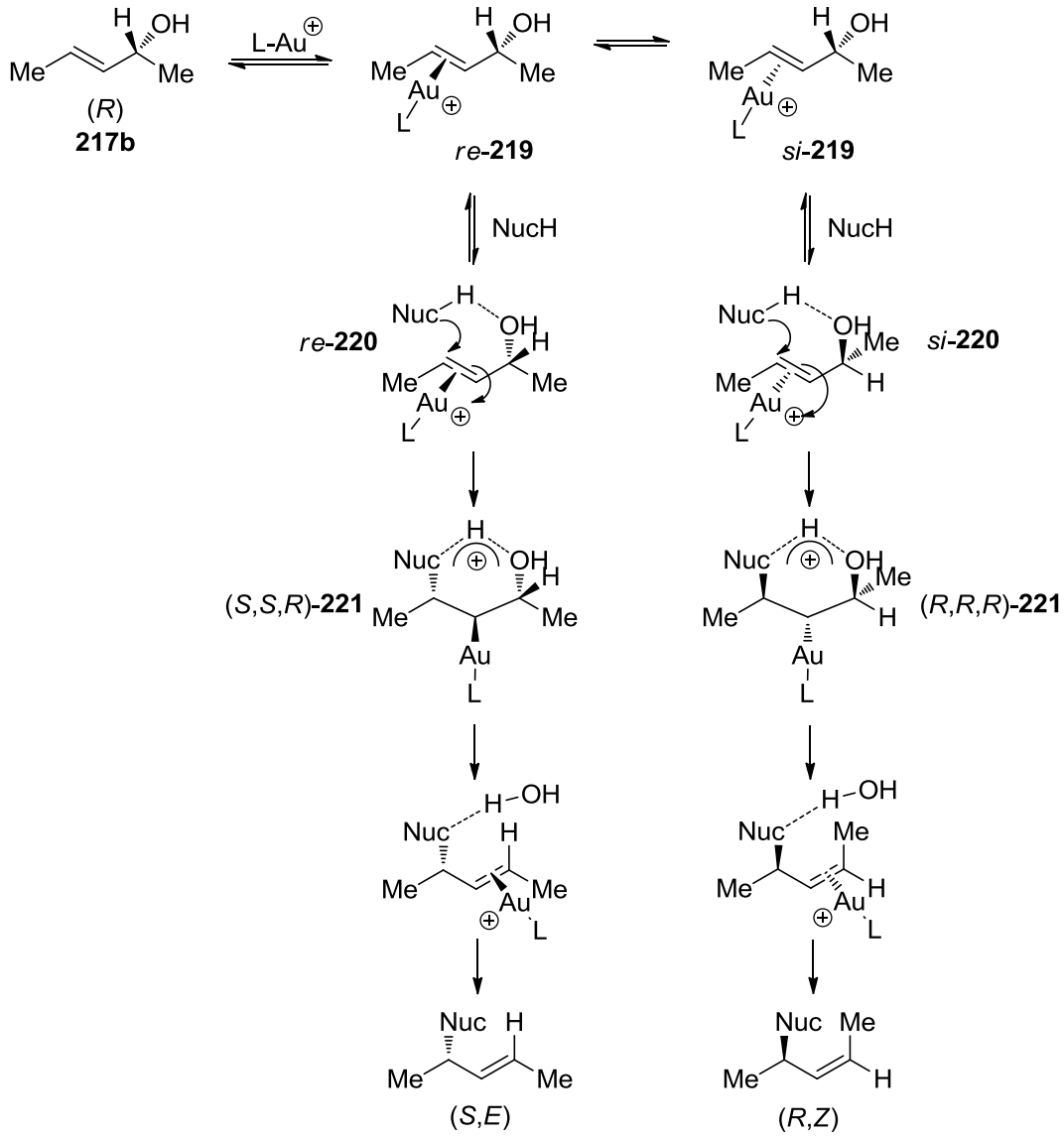
Scheme 5.3. Enantioselective gold-catalysed formation of tetrahydrocarbazoles by Bandini.

Gold-catalysed intermolecular reaction of allylic alcohols with amines have been shown to work,[17-19] but so far there are no examples of alcohols as nucleophiles due to the selectivity and poor nucleophilicity (*vide infra*).

An intermolecular transformation involving allylic alcohols and cyclic ureas was reported by Widenhoefer.[17] The products are that of a formal S_N2' pathway, and chirality transfer was achieved to great effect (Scheme 5.4). The authors noted that in the products of the reaction, *E* and *Z*-isomers gave opposing *S* and *R* enantioselectivities. This can be attributed to the proposed mechanism given by the authors (Scheme 5.5).



Scheme 5.4. Chiral transfer allylation of 1-methylimidazolidin-2-one by Widenhoefer.



Scheme 5.5. Widenhoefer's proposed mechanism for formation of opposing enantiomers.

The proposed mechanism for the stereochemical outcome of Widenhoefer's amination reaction, as shown in Scheme 5.5, begins with the formation of gold(I) π-alkene complexes (*si*-**219** and *re*-**219**). Hydrogen bonding then facilitates the delivery of the nucleophile (*si*-**220** and *re*-**220**), leading to attack at the activated alkene. Cyclic

alkyl-gold transition states (*S*,*S*,*R*)-**221** and (*R*,*R*,*R*)-**221** are formed, which undergo elimination of water and gold(I) to achieve (*S*,*E*) and (*R*,*Z*) products. The favoured (*S*,*E*)-product is probably formed due to the minimised steric interactions experienced in intermediate **221**. The interaction between gold and the methyl group in a *cis*-configuration to one another in (*R*,*R*,*R*)-**221** would be disfavoured.

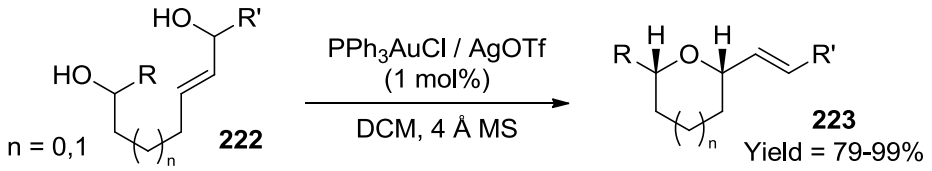
The *Z*-isomer of the starting material (**217b**) should produce the opposite (*R*, *E*) product as the major isomer following this mechanism, and that is indeed what is observed.

5.1.2 Allylic Etherification Reactions

5.1.2.1 Intramolecular Allylic Etherification Reactions

In terms of allylic etherification with gold and allylic alcohols, the work has solely been *intramolecular* and mainly carried out by Aponick and co-workers.[20-26]

Aponick and co-workers reported the gold(I)-catalysed cyclisation of monoallylic diols **222**.[20, 21, 23] The reaction produces tetrahydropyrans **223** (allylic ethers) in excellent yields, with catalyst loading as low as 0.1 mol% (Scheme 5.6). The products demonstrate the high diastereoselectivity of the reaction, achieving up to >25:1 in favour of the 2,6-*cis* product.



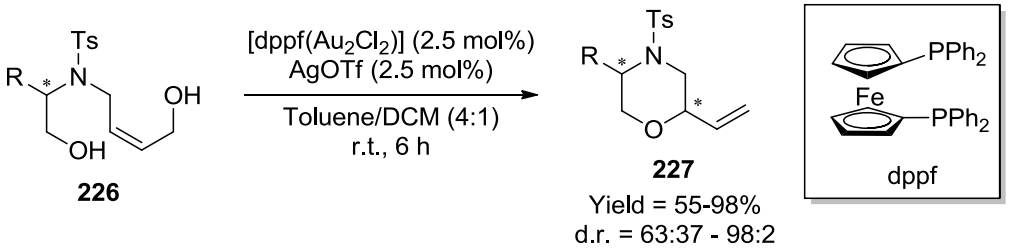
Scheme 5.6. Gold(I)-catalysed cyclisation of monoallylic diols by Aponick.

Control reactions were performed to deduce whether the reaction followed a cationic pathway. The mechanism is believed to proceed through an S_N2' pathway; in which the gold catalyst activates the alkene functionality. Ring closure can then occur through nucleophilic attack, followed by elimination of water and regeneration of the active catalyst.[27]

Since this methodology provided excellent stereocontrol, it was extended further for use in the synthesis of (+)-isoaltholactone.[28] This natural product is thought to inhibit breast cancer cell growth. The author's route to the desired compound included a key step involving Aponick's gold-catalysed cyclisation step (Scheme 5.7). Although a 1:1:1 d.r. was obtained of **225**, all three products could be carried forward to yield the desired (+)-isoaltholactone.

Scheme 5.7. Key gold-catalysed ring formation step in the synthesis of (+)-isoaltholactone.

In an extension to Aponick's ring closing etherification method, Bandini and co-workers reported a procedure for the synthesis of functionalised 2-vinyl-morpholines **227** (Scheme 5.8).[29] The reaction is highly stereoselective, with d.r. ratios up to 98:2. Several enantioselective reactions were also described by Bandini, with the best e.e. of product being 95%.



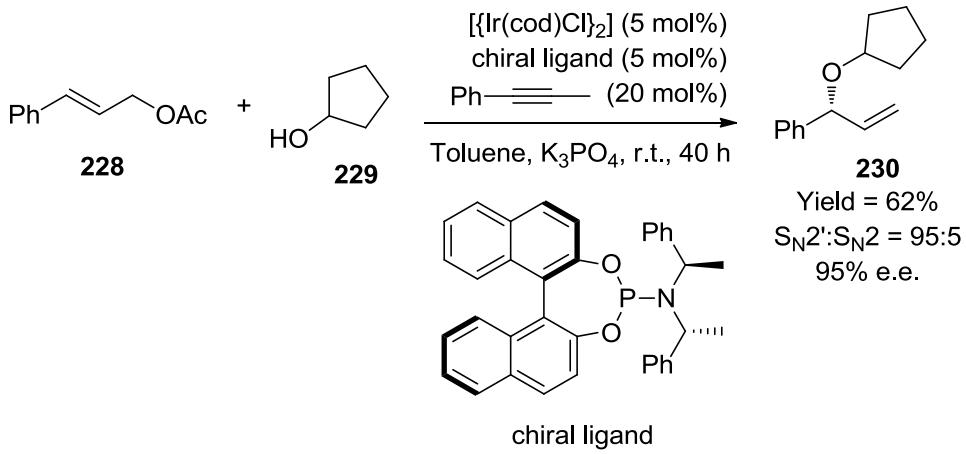
Scheme 5.8. Formation of 2-vinyl-morpholines *via* allylic etherification by Bandini.

So far Aponick and Bandini's work focuses on intramolecular formation of allylic ethers. However, it is highly desirable to achieve the more demanding intermolecular reactions.

5.1.2.2 Intermolecular Allylic Etherification Reactions

Although the Tsuji-Trost reaction is well known for *N*-nucleophiles, the analogous reaction with *O*-nucleophiles is usually hampered by the poor nucleophilicity of the alcohols. Therefore, the alcohols (as well as the allylating reagent) usually need to be activated.

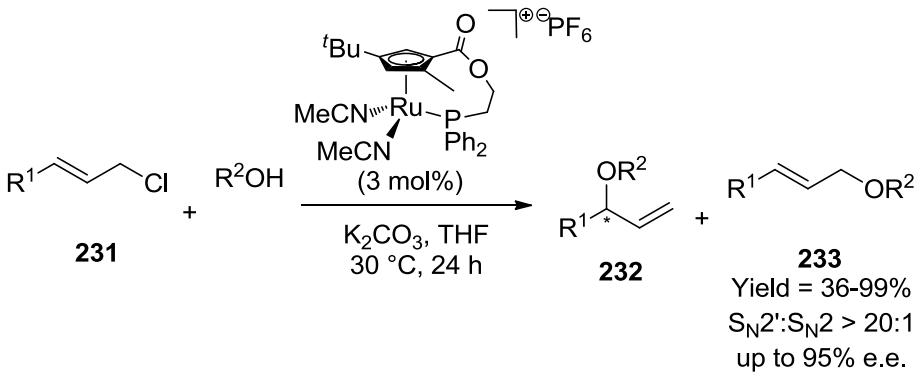
One of the best examples of allylic etherification is an iridium-catalysed intermolecular reaction reported by Hartwig in 2008, achieving the enantioselective synthesis of allylic ethers **230** from a formal S_N2' reaction (Scheme 5.9).[30]



Scheme 5.9. Iridium-catalysed allylic etherification by Hartwig.

Although this work is a major advance in the intermolecular formation of allylic ethers, there are some limitations to the reaction. The allylic substrate has been activated using an acetate group **228**, known to be a much better leaving group compared to an alcohol. The reaction must be carried out in a glovebox, which limits its practicality. There are also several additives present in the reaction, one is a strong base K_3PO_4 (to activate alcohol **229** to the better alkoxide nucleophile) and the other is an alkyne (to supress isomerisation of the products). The reaction scope is also limited to *primary* allylic acetate substrates, such as **228**.

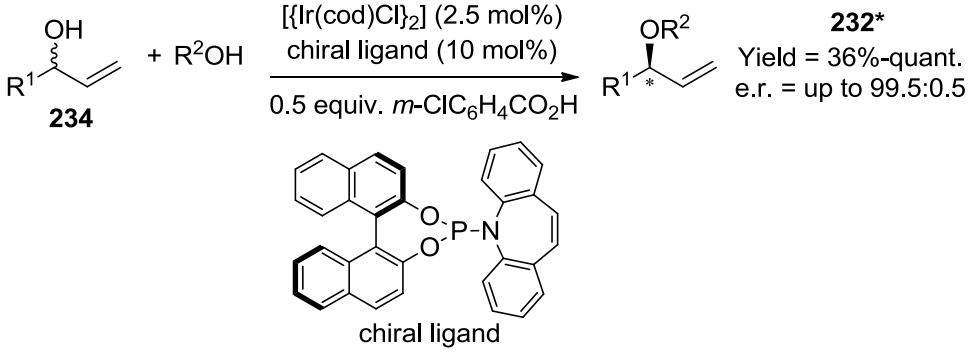
In the same year, an intermolecular ruthenium catalysed regio- and enantioselective allylic etherification reaction was also reported by Onitsuka and co-workers (Scheme 5.10).[31] The scope of the reaction includes primary nucleophile alcohols, as well as aromatic alcohols such as phenol.



Scheme 5.10. Ruthenium catalysed allylic etherification by Onitsuka.

The reaction requires the use of an activated allylic substrate **231** (allylic chloride), as well as K_2CO_3 as a base to form the more nucleophilic alkoxide. Regioselectivites are excellent (with the formal S_N2' product **232** being the major isomer), and high enantioselectivies are obtained. Once again, the substrate scope is limited to primary allylic chlorides, and to aromatic or primary alcohol nucleophiles.

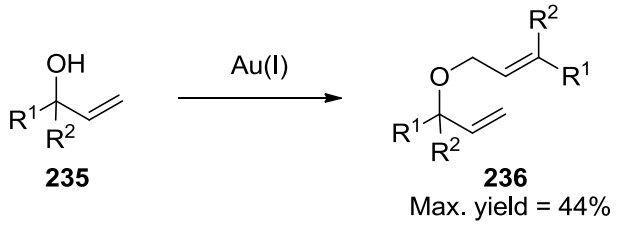
A further improvement was recently reported by Carreira and co-workers, in which an alcohol is reacted with an unactivated nucleophile alcohol enantioselectively.[32] Interestingly, however, the regioselectivity is completely inversed and the formal S_N2 product is observed (Scheme 5.11). The enantioselectivities achieved are excellent, along with yields and regioselectivities. A limitation is, again, observed with the scope of the reaction. Now only secondary allylic alcohols **234** can be utilised. A Brønsted acid additive must also be included in the reaction to activate the allylic alcohol substrate toward nucleophilic attack.



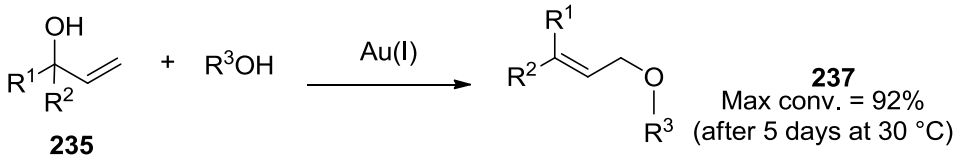
Scheme 5.11. Enantioselective iridium-catalysed allylic etherification by Carreira.

5.2 Project Aim

Previous work carried out within the Lee Group showed that allylic alcohols **235** would react under gold(I)-catalysed conditions (Scheme 5.12), to form allylic ether **236**. It was soon discovered that addition of a different alcohol nucleophile (R^3OH) allows for the more challenging intermolecular allylic etherification to produce **237** (Scheme 5.13).[33]



Scheme 5.12. Self-reaction of allylic alcohols under gold(I)-catalysed conditions.



Scheme 5.13. Desired gold(I)-catalysed allylic etherification of unactivated allylic alcohols.

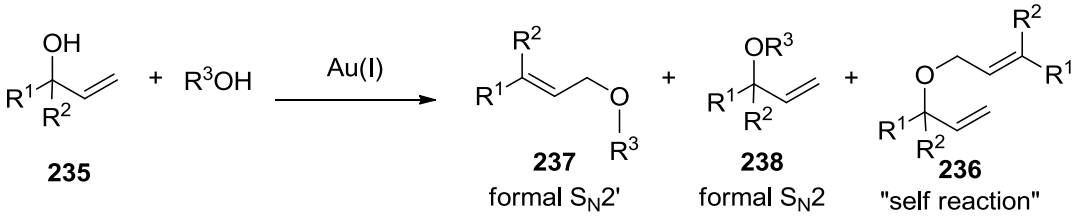
The aim of the project is to develop a regioselective and stereoselective allylic etherification method, catalysed by gold(I) (Scheme 5.13). Previous methods, as discussed above, have enlisted the use of additives or substrate activation to enable allylic etherification. However, it is desirable to develop a method in which no additives are added, and the substrates (both the allylating reagent and alcohol) are completely unactivated. Furthermore, the use of gold(I) chemistry should allow for mild and practical (in air) reactions to address some of the practicality issues (e.g. glovebox) of previous methods.

Once an optimised reaction has been developed after a series of screening experiments, a substrate scope will be carried out of both allylic alcohols and nucleophile alcohols. Previous allylic etherification methods have been limited in their substrate scope, therefore wider scopes of these substrates would be highly desirable (primary, secondary and tertiary alcohols).

5.3 Results & Discussion

5.3.1 Reaction Optimisation & Scope

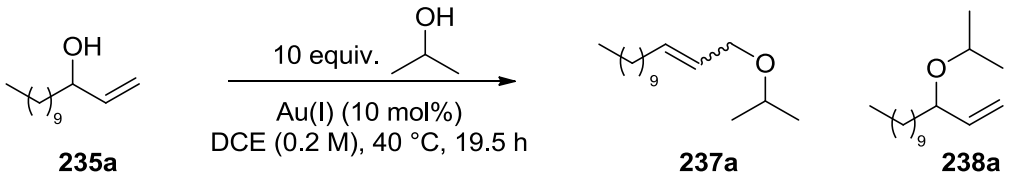
Initially the reaction was riddled with challenges that had to be overcome (Scheme 5.14). Unactivated allylic alcohols and nucleophile alcohols generally suffer from low reactivity and the fact that the reactive substrate is itself an alcohol means that self-reaction (of **235**, for example Scheme 5.12) is possible. Regioselectivity also had to be improved from the initial experiments (**237**:**238**), as well as stereoselectivity (*E vs. Z*) of **237**.



Scheme 5.14. Initial unoptimised conditions of gold(I)-catalysed allylic etherification.

A series of optimisation studies were performed on allylic alcohol **235a** to improve the reaction, but at the same time it was desirable to keep the reaction conditions fairly mild. Firstly, a catalyst screen was carried out to determine the best gold-species for the reaction using a secondary allylic alcohol (Table 5.1).

Table 5.1. Gold(I) catalyst screen for allylic etherification.



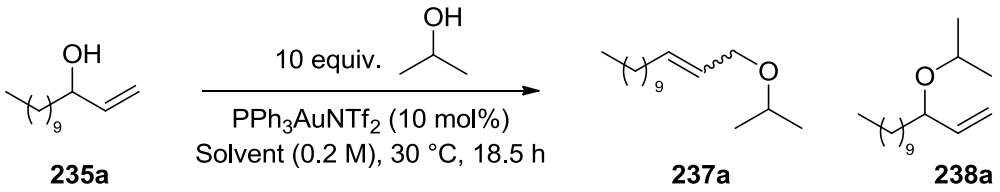
235a **237a** **238a**

Entry	**Catalyst**	**Isolated Yield**	***E*:*Z***	**237a:238a (S_N2':S_N2)**[a]
1	**6** / AgOTf	63%	3.4:1	≈ 10:1
2	PPh_3AuCl / AgOTf	47%	5.3:1	≈ 16:1
3	**1**	59%	6.6:1	≈ 11:1
4	PPh_3AuNTf_2	80%	6.1:1	> 20:1
5	(IPr)AuCl / AgOTf	36%	5.4:1	≈ 10:1

[a] Determined by ^{1}H NMR analysis.

All catalysts tested showed a good to excellent regioselectivity in the reaction, with the formal S_N2' product **237a** being the major isomer present. A phosphite ligand on the gold gives a good yield, however a poor *E*:*Z* ratio (entry 1). The *E*:*Z* ratio is noticeably improved when the ligand is changed to a phosphine (entries 2-4), however only the commercially available PPh_3AuNTf_2 catalyst showed an improvement in yield as well as regio- and stereoselectivity (entry 4). The best catalyst was then carried forward to be used in a solvent screen (Table 5.2). A lower temperature of 30 °C was employed for the screen since DCM would be at its boiling point at 40 °C.

Table 5.2. Solvent screen for allylic etherification.



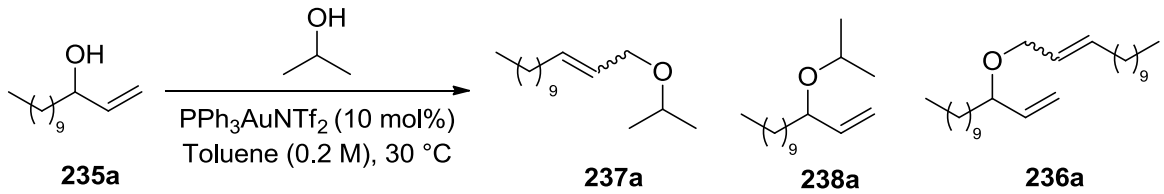
Entry	Solvent	Conversion [a]	*E*:*Z* [a]	237a:238a (S_N2':S_N2) [a]	Comments
1	DCM	38%	4.8:1	≈ 15.7:1	
2	Chloroform	26%	4.1:1	≈ 19:1	
3	DCE	53%	≈ 6.2:1	≈ 10:1	Traces of unidentified side-product
4	Toluene	42%	8:1	> 20:1	Cleaner than chlorinated solvents
5	Dioxane	14%	N/D[b]	≈ 11.5:1	Unidentified side-product visible
6	THF	17%	3.3:1	> 20:1	Unidentified side-product visible
7	Acetonitrile	0	N/A	N/A	
8	DMF	0	N/A	N/A	

[a] Determined by ^{1}H NMR analysis. [b] Not determined due to poor conversion.

The conversion of starting material to product varies significantly depending on the solvent. The reaction appears to be suppressed with increasing solvent polarity; in fact the reaction is completely shut down using acetonitrile and DMF (entries 7 & 8). 1,2-Dichloroethane was shown to have the highest conversion (entry 3), however there were signs of an unidentified side-product in the crude ^{1}H NMR spectrum. Toluene showed a reasonable conversion, with the best *E*:*Z* ratio and regioselectivity (entry 5). Using toluene as a solvent also produced a much cleaner reaction, with no side-products visible in the crude NMR spectrum. Hence, toluene was selected as the solvent for this reaction.

Thus far the reaction utilised 10 equivalents of the nucleophile alcohol, in order to avoid self-reaction. Therefore it was desirable to try lower this value to reduce waste within the reaction conditions (Table 5.3).

Table 5.3. Equivalents of nucleophile alcohol for allylic etherification.



235a **237a** **238a** **236a**

Entry	Equiv. ^{i}PrOH	Time	Conversion [a]	*E*:*Z* [a]	237a:238a (S_N2':S_N2) [a]	237a:236a (S_N2':self-reaction) [a]
1	1	1 day	17%	N/D	> 20:1	N/D
		3 days	42%	8:1	> 20:1	≈ 5:1
2	2	1 day	19%	N/D	≈ 15:1	N/D
		3 days	45%	7:1	≈ 9.5:1	≈ 7:1
3	3	1 days	26%	N/D	> 20:1	N/D
		3 days	54%	8:1	≈ 11.5:1	≈ 8:1
4	4	1 day	25%	N/D	> 20:1	> 20:1
		3 days	56%	8:1	> 20:1	> 20:1
5	5	1 day	26%	N/D	> 20:1	> 20:1
		3 days	57%	9:1	> 20:1	> 20:1

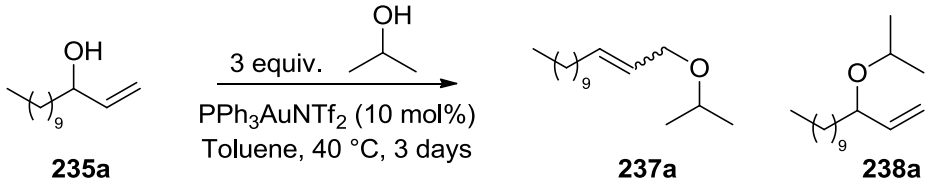
[a] Determined by ^{1}H NMR analysis.

Severely reducing the number of nucleophile alcohol equivalents was detrimental to the reaction (entries 1 & 2). The *E*:*Z* ratios could not be determined for all the 1 day results due to the poor conversion, and the inability to accurately measure the ratio because of baseline noise in the NMR spectrum. Going as low at 1 equivalent (entry 1) proved unfruitful as the conversion from starting material was poor after 1 day. Increasing the reaction time to 3 days was helpful in improving the conversion, however the self-reaction product **236a** of the allylic alcohol was observed in a 5:1 ratio with the desired product **237a**. The self-reaction product **236a** remains visible up to 3 equivalents of 2-propanol (entries 2 & 3), but is completely eradicated when ^{i}PrOH equivalents above 4 are used (entries 4 and 5). The decision was taken to select 5 equivalents of

nucleophile alcohol as the optimum conditions, because although the conversions are comparable with 4 equivalents, there is an improvement in the *E*:*Z* ratio.

In order to improve the conversion of the reaction, it was decided that a concentration screen should be carried out (Table 5.4).

Table 5.4. Concentration screen for allylic etherification.



235a **237a** **238a**

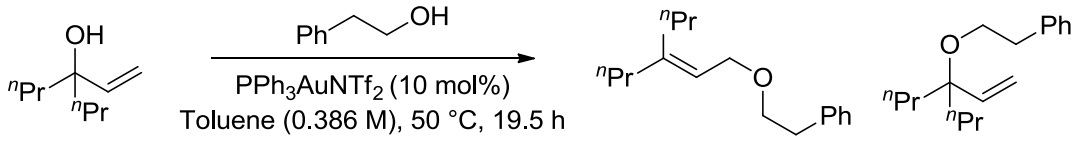
Entry	**Concentration (mol L^{-1})**	**Conversion** [a]	***E*:*Z*** [a]	**237a:238a (S_N2':S_N2)** [a]
1	0.05	7%	≈ 1:0	> 20:1
2	0.1	20%	8:1	≈ 16:1
3	0.2	52%	10:1	≈ 15:1
4	0.5	80%	8:1	≈ 16:1
5	1.0	86%	7:1	≈ 14:1

[a] Determined by ^{1}H NMR analysis.

Lowering the concentration below 0.2 mol L^{-1} reduces the overall conversion of the reaction (entries 1 & 2). It is clear that with increasing concentration, however, the conversion improved (entries 4 & 5). Concentrations above 1.0 mol L^{-1} were not attempted due to the very small amount of solvent that would be used compared to nucleophile alcohol. It did become apparent that the regioselectivity of this reaction was still not fully perfected, with some of the formal S_N2 product **238a** being observed. At this point, it was decided that a tertiary allylic alcohol would be used as the substrate. This would significantly reduce the probability of any self-reaction product forming, but would be interesting to investigate whether the increased steric bulk of the substrate would have any effect on the regio- and stereoselectivities.

Next, we wanted to also look at the feasibility of using tertiary allylic alcohols in the reaction. A small number of further optimisation studies were therefore performed on tertiary allylic alcohol **235b**. Initially, alcohol nucleophile equivalents were probed (Table 5.5).

Table 5.5. Equivalents of nucleophile alcohol screen with tertiary allylic alcohol.



235b **237b** **238b**

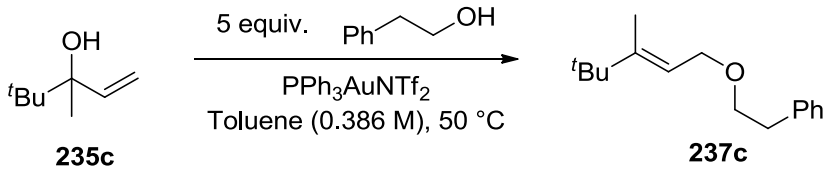
Entry	**Equiv. Alcohol**	**Conversion** [a]	**237b:238b (S_N2':S_N2)** [a]
1	1	> 95%	N/D[b]
2	2	> 95%	15:1
3	3	> 95%	> 20:1
4	5	100%	> 20:1

[a] Determined by ^{1}H NMR analysis. [b] Not determined due to messy spectrum.

Overall switching from a secondary to a tertiary allylic alcohol **235b** proved greatly beneficial. There were fewer issues with conversion, and S_N2':S_N2 ratio remained at excellent levels with 5 equivalents of the nucleophile alcohol (entry 4). Lowering the number of alcohol equivalents had little effect on the overall conversion from starting material; however it is evident that the regioselectivity decreases. In fact, using one equivalent of nucleophile alcohol resulted in a very messy spectrum with self-reaction product visible.

Up to this point the reaction required 10 mol% of gold catalyst. It was therefore desirable to attempt to limit the amount of gold used in the reaction (Table 5.6).

Table 5.6. Catalyst loading screen for allylic etherification.



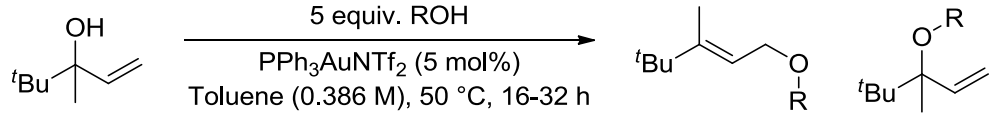
235c **237c**

Entry	Catalyst Loading	Time (h)	Isolated Yield
1	10 mol%	17.5	57%
2	5 mol%	17.5	62%
3	5 mol%	29.5	76%

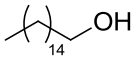
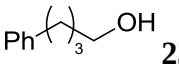
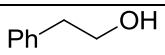
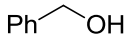
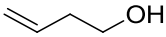
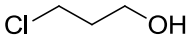
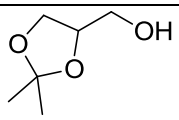
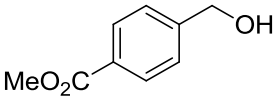
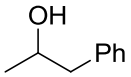
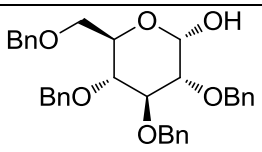
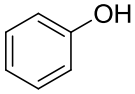
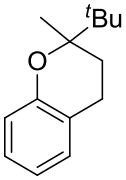
The formal S_N2 product **238c** was not observed in any of these reactions. Reducing the catalyst loading to 5 mol% improved the overall yield of the reaction (entry 2). Taking this forward and increasing the reaction time also had a beneficial effect on the isolated yield of **237c** (entry 3). The decision was taken to leave all reactions for over 24 hours, to allow for the best yield to be achieved.

With these optimised conditions in hand, the generality of the reaction was tested. Tertiary allylic alcohol **235c** was selected as the substrate to test the scope of alcohol nucleophiles (Table 5.7). The results were very pleasing, giving excellent regioselectivities in favour of the formal S_N2' product **237c**, and excellent stereoselectivity, with exclusively *E*-isomer observed.

Table 5.7. Substrate scope of alcohol nucleophiles.



235c **237** **238**

Entry	ROH	Product	*E* : *Z*[a]	237:238 (S_N2':S_N2)[a]	Isolated Yield
1		**237d**	> 20:1	> 20:1	83%
2	 **239**	**237e**	> 20:1	12:1	75%
3		**237c**	> 20:1	> 20:1	76%
4		**237f**	> 20:1	> 20:1	77%
5		**237g**	> 20:1	> 20:1	75%
6		**237h**	> 20:1	> 20:1	65%
7		**237i**	> 20:1	> 20:1	77%
8		**237j**	> 20:1	> 20:1	74%
9		**237k**	> 20:1	> 20:1	71%
10		**237l**	> 20:1	> 20:1	57%[b]
11[c]		**237m**	> 20:1	> 20:1	52%[d]
12		 **240a**	N/A	N/A	53%

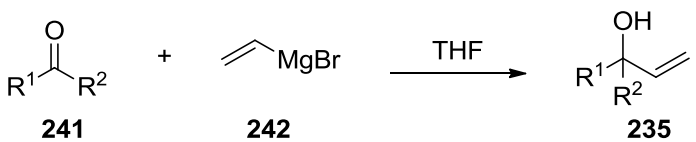
[a] Determined by ^{1}H NMR analysis. [b] Volatile product. [c] Chloroform as solvent. [d] α:β 3:1.

The reaction proceeds well with a wide range of primary nucleophile alcohols (entries 1-8), giving excellent regio- and stereoselectivities. However, an unexplained drop in regioselectivity is observed when alcohol **239** is used (entry 2). The reaction was shown to be extremely mild, demonstrated by its superb functional group tolerance, including: an isolated alkene (entry 5), an electrophilic alkyl chloride (entry 6), an acid-sensitive acetal group (entry 7) and a base sensitive ester (entry 8). Strikingly, even a hemiacetal in the form of a protected sugar is tolerated (entry 11). It is perhaps worth noting that these functional groups would not be tolerated in previous allylic etherification reactions, which employ the use of strong acids[34] or bases.[30]

Moving away from primary nucleophile alcohol, and using a secondary alcohol gives a good 71% yield (entry 9). Even when an extremely sterically hindered alcohol was used, the reaction proceeded to a decent 57% yield (entry 10). The product **237l** is thought to be volatile, so some mass may have been lost throughout the purification procedure. These results were pleasing since it demonstrated that primary, secondary and tertiary nucleophile alcohols could be used, representing the wide substrate scope of this reaction.

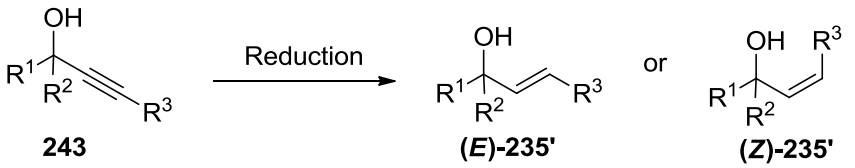
The greatest surprise was the product acquired when phenol was used as a nucleophile (entry 12). Instead of the expected allylic etherification product, chroman **240** was obtained. It was suspected that this formed through a Friedel-Crafts type allylation mechanism, followed by cyclisation (see Section 5.3.3). An analogous reaction using molybdenum catalysis had previously been reported, however this required heating to 150 °C using a microwave.[35]

Next, the attention was turned to the allylic alcohol scope (Table 5.8). The allylic alcohol substrates were formed *via* known procedures; Grignard additions to aldehydes or ketones **241** (Scheme 5.15), or reduction of a propargylic alcohols **243** (Scheme 5.16).



241 **242** **235**

Scheme 5.15. Vinyl-Grignard addition to aldehydes or ketones.



243 **(*E*)-235'** **(*Z*)-235'**

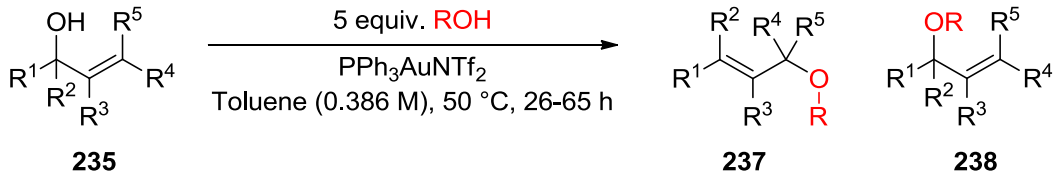
Scheme 5.16. Reduction of propargylic alcohols to γ-substituted allylic alcohols.

As shown in Table 5.8, the scope is wide ranging, the yield improves with increasing steric bulk going from methyl to *n*-propyl to cyclohexyl substituents (entries 1-3). Introducing the potential for *E*:*Z* isomers, it was shown that stereoselectivity decreases going from *tert*-butyl to phenyl to cyclohexyl substituents (entries 4-6), although the *E*-isomer is still always favoured. Secondary allylic alcohols were also tested, with both primary and secondary nucleophile alcohols (entries 7-12). Yields remained high (61-91%) and *E*-isomer selectivity still dominated.

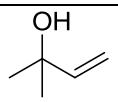
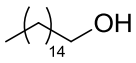
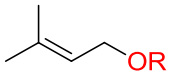
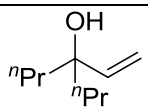
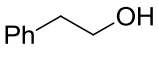
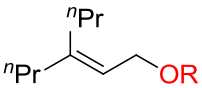
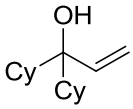
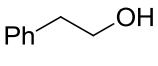
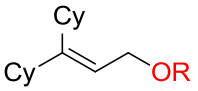
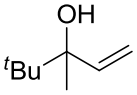
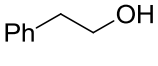
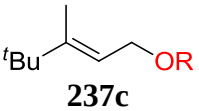
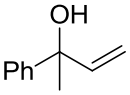
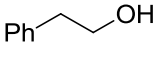
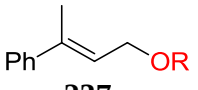
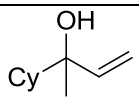
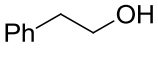
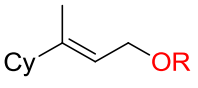
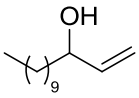
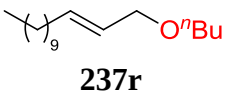
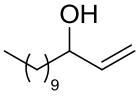
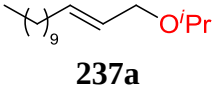
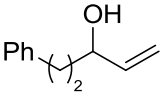
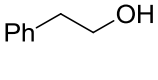
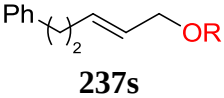
Substitution around the allylic alcohol alkene was also investigated. If a methyl group is added in the γ-position **235j**, the stereoselectivity was found to be high (20:1 *E*:*Z*), as was the regioselectivity (14:1) (entry 11). When the allylic alcohol was substituted in the β-position **235k**, stereoselectivity remained excellent, however the regioselectivity is severely reduced to 1:1 (entry 12).

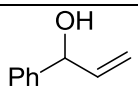
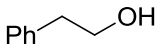
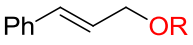
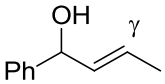
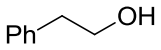
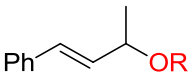
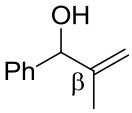
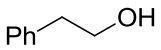
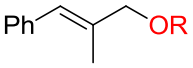
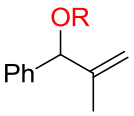
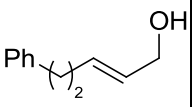
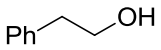
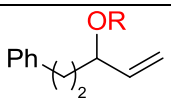
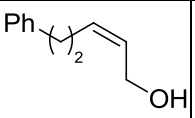
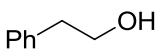
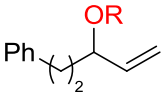
To conclude the list, primary allylic alcohols were examined (entries 13 & 14). The *trans*-isomer **235l** (entry 13) showed higher yield, as well as increased regioselectivity compared to the *cis*-isomer **235m** (entry 14). Due to both reagents being primary alcohols, there was competition from the self-reaction. Hence, the reaction with the *trans*-isomer also gave trace amounts of self-reaction product (<5%), and the reaction with the *cis*-isomer produced slightly more (7%).

Table 5.8. Substrate scope of allylic alcohols.



235 **237** **238**

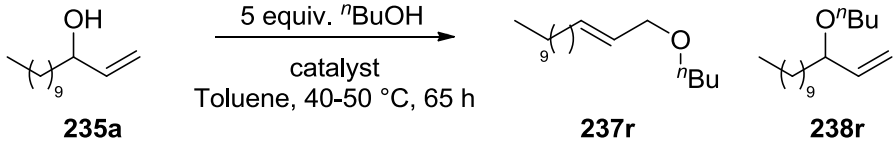
Entry	Allylic Alcohol	ROH	Product	*E* : *Z*[a]	237:238 (S_N2':S_N2)[a]	Isolated Yield
1[b]	 **235d**		 **237n**	N/A	5:1	62%
2[b]	 **235b**		 **237b**	N/A	Only **237**	78%
3[b]	 **235e**		 **237o**	N/A	Only **237**	91%
4[b]	 **235c**		 **237c**	> 20:1	Only **237**	76%
5[b]	 **235f**		 **237p**	6:1	Only **237**	67%
6[b]	 **235g**		 **237q**	5:1	> 20:1	71%
7[c]	 **235a**	^{n}BuOH	 **237r**	6:1	10:1	82%
8[c]	 **235a**	^{i}PrOH	 **237a**	8:1	11:1	91%
9[c]	 **235h**		 **237s**	7:1	4.5:1	69%

10 [c]	 **235i**		 **237t**	17:1	Only **237**	61%
11 [c]	 **235j**		 **237u**	20:1	14:1	68%
12 [b]	 **235k**		 **237v**  **238v**	> 20:1 **237v**	1:1	74% (**237** + **238**)
13 [b]	 **235l**		 **237w**	N/A	6:1 [d]	63%
14	 **235m**		 **237w**	N/A	4:1 [e]	40%

[a] Determined by ^{1}H NMR analysis. [b] PPh_3AuNTf_2 (5 mol%), 50 °C. [c] PPh_3AuNTf_2 (10 mol%), 50 °C. [d] Self-reaction product observed in <5% yield. [e] Self-reaction product observed in ~7% yield.

To fully determine that this reaction was indeed gold-catalysed, a series of controls were carried out (Table 5.9). Addition of a hindered base, to quench trace acid present in the reaction, still produced the desired product in excellent yield (entry 1). An acid-catalysed reaction was attempted using $HNTf_2$ as a catalyst, only succeeded in producing trace amounts of product (entry 2). These two results indicate that trace acid is not responsible for carrying out the reaction. A final control experiment was run, using catalytic amounts of $AgNTf_2$ (entry 3). Interestingly, this gave roughly 15% conversion to the opposite regioisomer **238r**. Taking all these control experiments into account, it can be concluded that it is gold catalysing the reaction.

Table 5.9. Control reactions.

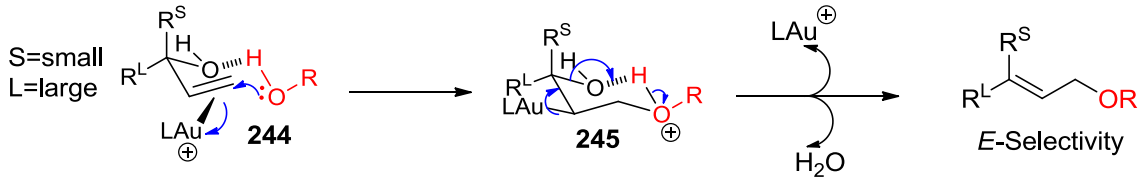


235a 237r 238r

Entry	Catalyst	Catalyst Loading	Result[a]	Isolated Yield
1[b]	PPh_3AuNTf_2 + 2,6-di-*tert*-butylpyridine	10 mol%	100% conversion to **237r** (S_N2')	82% (*E*:*Z* = 6:1)
2[c]	$HNTf_2$	1 mol%	<5% conversion to **237r** (S_N2')	N/D
3[c]	$AgNTf_2$	5 mol%	15% conversion to **238r** (S_N2)	N/D

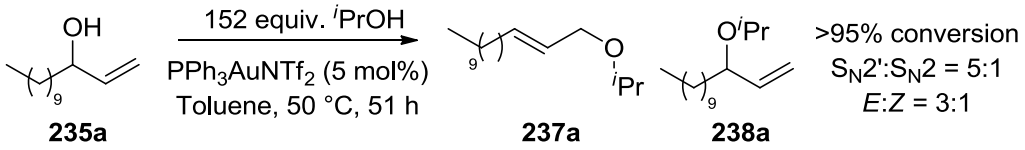
[a] Determined by ^{1}H NMR analysis. [b] 40 °C. [c] 50 °C.

The excellent regio- and stereoselectivity can be explained by the proposed six-membered transition state in the reaction mechanism (Scheme 5.17).[26] The gold(I) catalyst activates the alkene bond of the allylic alcohol toward nucleophilic attack. A chair-like six-membered cyclic ring is set-up, and nucleophile alcohol is delivered to the reactive centre, aided by hydrogen bonding as shown in **244**. Demetallation and elimination of water can then occur to regenerate the active catalyst, and produce the desired product. The *E*-selectivity can be attributed to the chair-like six-membered transition state, where the bulky R group (R^L) is forced into the equatorial position.



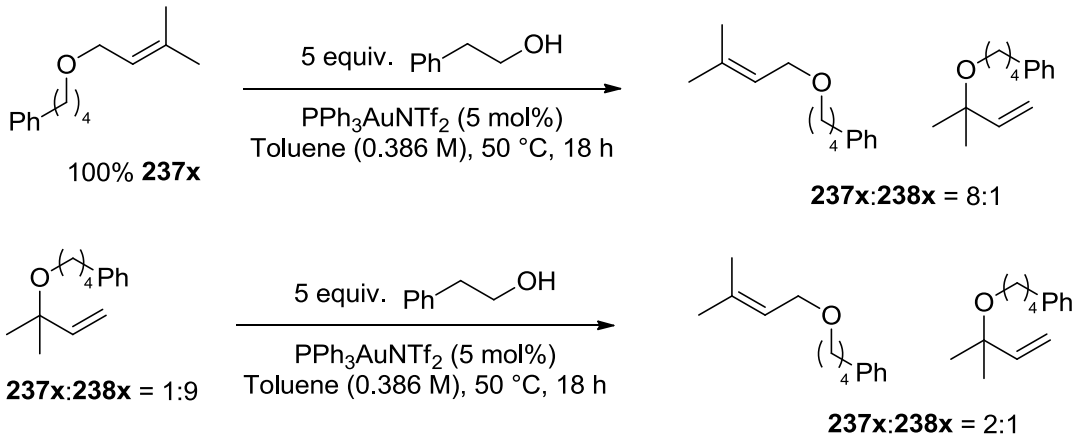
Scheme 5.17. Proposed mechanism for the gold-catalysed allylic etherification.

A control reaction was attempted to gain further evidence for this proposed mechanism. A reaction was carried out in neat ^{i}PrOH (Scheme 5.18). The result was > 95% conversion, however the *E*:*Z* ratio dropped significantly to roughly 3:1. The regioselectivity (**237a**:**238a**) also dropped to 5:1. This is probably explained by the hydrogen-bonding in the chair-like transition state being perturbed by the protic solvent.



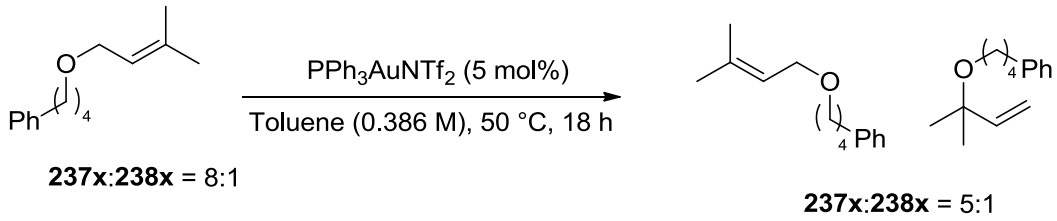
Scheme 5.18. Allylic etherification in neat alcohol.

In order to determine if the formal S_N2 product **238** is obtained from direct attack of the allylic alcohol **235**, or from further reaction of the formal S_N2' product **237**, several experiments were carried out. The formal S_N2' and S_N2 products (**237** & **238** respectively) were both resubjected to the reaction conditions (Scheme 5.19).



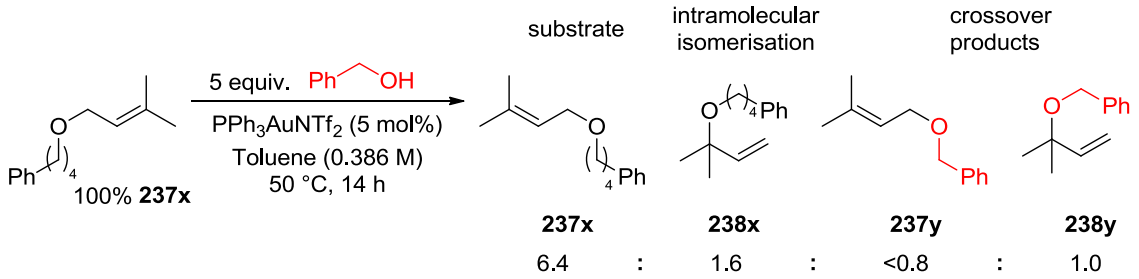
Scheme 5.19. Allylic etherification products resubjected to reaction conditions.

The products were not isolated, and the ratios were determined by ^{1}H NMR analysis. It was evident that both the formal S_N2' and S_N2 (**237x** & **238x**) products are isomerising to each other, catalysed by gold(I). To establish whether this process requires the presence of excess alcohol, a further experiment was run without additional alcohol (Scheme 5.20).



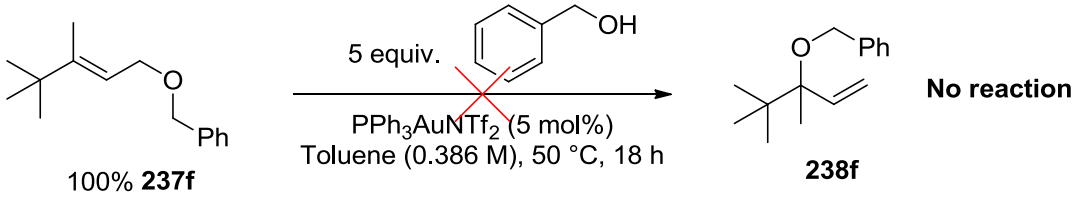
Scheme 5.20. Isomerisation experiment without excess alcohol.

It is clear from Scheme 5.20 that the isomerisation occurs without the need for excess alcohol; however it does appear to be suppressed. A final isomerisation control reaction was carried out in order to determine whether the process was intra- or intermolecular (Scheme 5.21). An alternative nucleophile alcohol was added, the hypothesis being that if there was cross-over of substituents then this would suggest an intermolecular process.



Scheme 5.21. Addition of a different nucleophile alcohol, crossover experiment.

This reaction demonstrated that there was indeed cross-over of nucleophile alcohols. The ratio of **237x**:**238x**:**237y**:**238y** was found to be 6.4 : 1.6 : <0.8 : 1. Although products **237y** and **238y** are both the minor products, it still confirmed that the reaction can be intermolecular, as well as intramolecular. This is true for the substrates which exhibit S_N2':S_N2 regioselectivity ratios for the original reaction (such as Table 5.8, entry 1). However, if no formal S_N2 product **238** is observed initially (such as Table 5.7, entry 4), then no isomerisation will take place when the product is resubjected to the reaction conditions (Scheme 5.22).

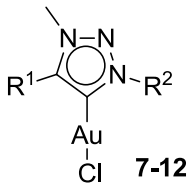


Scheme 5.22. Isomerisation attempt with allylic alcohol.

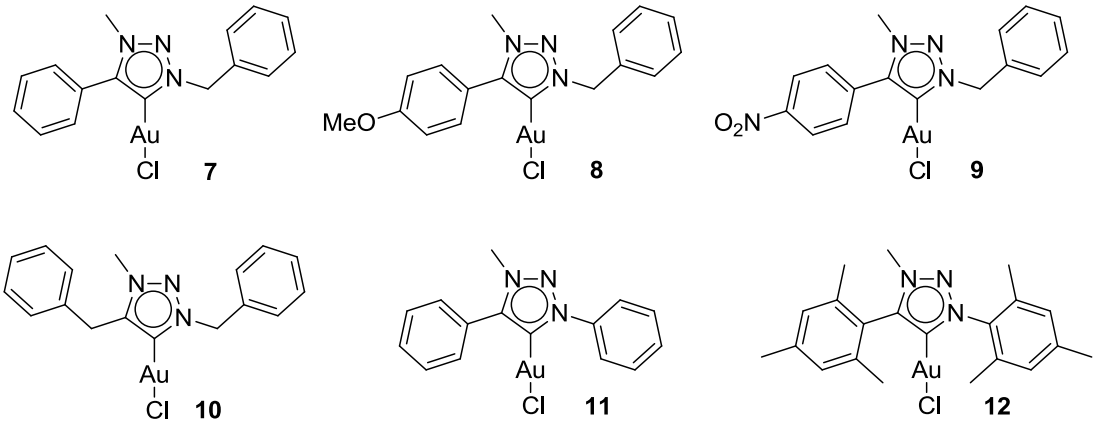
In conclusion, any formal S_N2 product **238** observed in the reaction is likely to be formed by isomerisation of the desired formal S_N2' product **237**, rather than by direct S_N2-type attack. In cases where the formal S_N2 side product **238** is observed (e.g. Table 5.8, entry 1), control experiments show that the isomerisation of **237** and **238** can occur, catalysed by gold(I). In cases where no formal S_N2 product **238** is observed in the reaction, control experiments show that this is because the desired formal S_N2' product **237** is stable to further isomerisation.

5.3.2 Gold(I) "Click" 1,2,3-triazolylidenes – Improving reaction conditions

As part of an on-going collaboration with the Crowley Group from the University of Otago, New Zealand, the Lee Group is committed to exploring the catalytic activity of novel gold(I) 1,2,3-triazolylidene (Trz) catalysts (Scheme 5.23).[36, 37] These catalysts are viewed as abnormal NHC-ligands or mesoionic systems, since there are no sensible neutral resonance structures that can be drawn.[38-41] These catalysts have been shown to be excellent ligands in gold(I)-catalysed reactions;[37, 42] and therefore a library of different catalysts were prepared by our collaborators for us to test in catalytic reactions (Scheme 5.24).

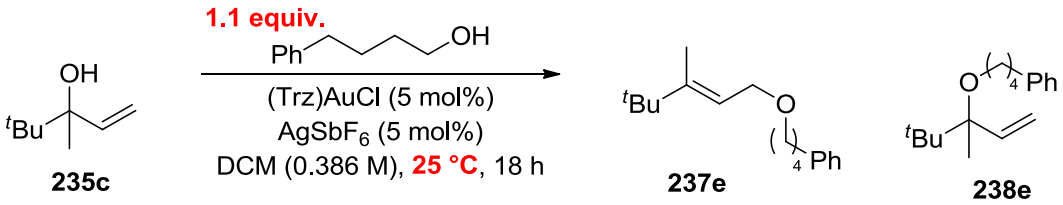


Scheme 5.23. General structure of (Trz)AuCl complexes.



Scheme 5.24. Library of (Trz)AuCl complexes tested for catalytic activity.

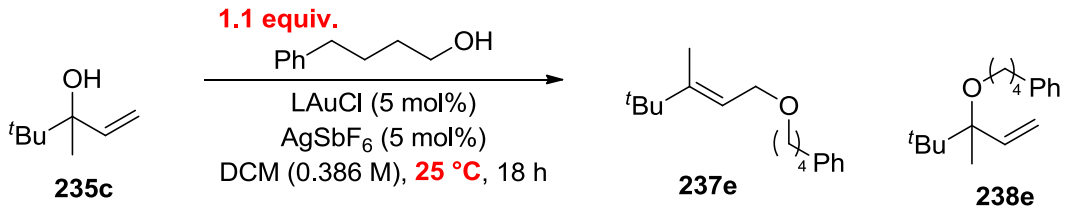
With this library of complexes, the effect of varying both the electronics (**7-9**) and the steric bulk (**10-12**) of the Trz ligand on catalytic activity can be examined. The gold(I)-catalysed allylic etherification reaction was selected to test the nature of the complexes (Scheme 5.25). In addition, it was hoped that the reactions conditions could potentially be improved using these novel catalysts. Abnormal NHC ligands are thought to be more donating than normal NHC and phosphine ligands,[36, 41] thus rendering the gold catalyst less electrophilic. Such tuning of reactivity can sometimes improve selectivities.



Scheme 5.25. Allylic etherification using gold(I) Trz catalysts.

Pleasingly, using the gold(I) Trz catalysts in this reaction not only allowed the use much milder conditions (25 °C compared to 50 °C), but also the equivalents of the nucleophile alcohol was severely reduced (1.1 equivalents, compared to 5 equivalents), Scheme 5.25. This is clearly desirable to avoid waste and improve atom economy. A screen of the various complexes was carried out using these newly improved conditions (Table 5.10).

Table 5.10. Gold(I) Trz catalyst screen for direct allylic etherification.



235c **237e** **238e**

Entry	LAuCl	237e:238e[a]	Isolated Yield of 237e	*E*:*Z*[a]
1	**7**	>20:1	74%	6:1
2	**8**	>20:1	76%	8:1
3	**9**	>20:1	64%	8:1
4	**10**	>20:1	67%	9:1
5	**11**	>20:1	67%	12:1
6	**12**	>20:1	66%	6:1
7	PPh_3AuNTf_2[b]	4:1	Incomplete reaction:[c] 3:4:1 **235c**:**237e**:**238e** 9% of self-reaction of **235c**	5:1
8	(IPr)AuCl	2.5:1	Incomplete reaction:[c] 3:2.5:1 **235c**:**237e**:**238e**	4:1
9	(IMes)AuCl	>20:1	70%	5:1
10	PPh_3AuCl	17:1	61%	4:1

[a] Determined by ^1H NMR analysis. [b] No $AgSbF_6$ added. [c] Using 2,3,5,6-tetrachloronitrobenzene as an internal standard.

All Trz complexes used resulted in good yields (entries 1-6), and are comparable to the 75% yield achieved from the original allylic etherification conditions (Table 5.7, entry 2). There is a marked improvement in the regioselectivity of the reaction, with all complexes showing an excellent >20:1 **237e**:**238e** ratio; compared to 12:1 from the original reaction conditions.

The reaction is somewhat sensitive to the electronics of the Trz ligands (entries 1-3), with the more electron-rich species **8** providing an 8:1 *E*:*Z* ratio (entry 2), up from 6:1 when using the parent species **7** (entry 1). Whereas moving to an electron deficient ligand **9** results in a drop in yield of the desired product (entry 3). Altering the overall steric bulk of the ligand appears to have little effect on the reaction (entries 4-6), with neither the yield nor regioselectivity varying, although the *E*:*Z* selectivity is affected.

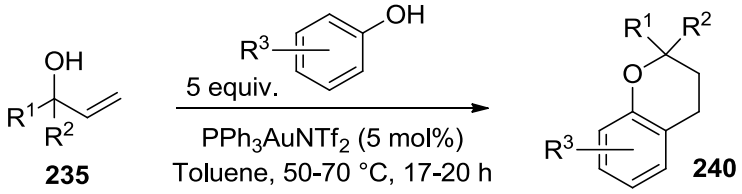
In order to gauge the activity of these catalysts with respect to other commonly used species, several reactions were performed (entries 7-10) under these new milder conditions. When the original etherification gold(I) catalyst, PPh_3AuNTf_2, is utilised under these conditions, the outcome is drastically worse (entry 7). Not only does the regioselectivity drop to 4:1, but there is also incomplete conversion from starting material (roughly 54% conversion from **235c**). In addition to this, 9% of the self-reaction product is also observed. This can be attributed to the absence of excess nucleophile alcohol required to retard the self-etherification reaction (*vide supra*).

The commercially available species containing NHC-ligands, (IPr)AuCl and (IMes)AuCl, were investigated as a comparison (entries 8 & 9). The (IPr)AuCl precatalyst resulted in a poor conversion and worse regio- and stereoselectivities (entry 8). In contrast, the (IMes)AuCl complex achieved a good 70% isolated yield of **237e**, along with excellent regioselectivity (>20:1) (entry 9). However, the stereoselectivity was less impressive (4:1) compared to that of the Trz species. As a final comparison, the PPh_3AuCl precatalyst was also studied (entry 10). It fared worse compared to the Trz species, with lower yield and selectivities obtained.

With these new conditions achieved, the reaction conditions had been significantly improved (milder 25 °C temperature and no need for excess alcohol nucleophile). Unfortunately, it was soon discovered that these conditions were not general. These conditions were only suitable for tertiary allylic alcohols with primary nucleophile alcohols. Outwith these substrates, little or no reaction was observed. Those substrates that did show reactivity resulted in extremely complex crude ^{1}H-NMR spectra. On steric grounds, this makes sense as the tertiary allylic alcohol (e.g. **235c**) is less likely to react with itself compared to less hindered allylic alcohols. At this stage, it is not entirely clear why the (Trz)Au catalysts work so well for this substrate combination.

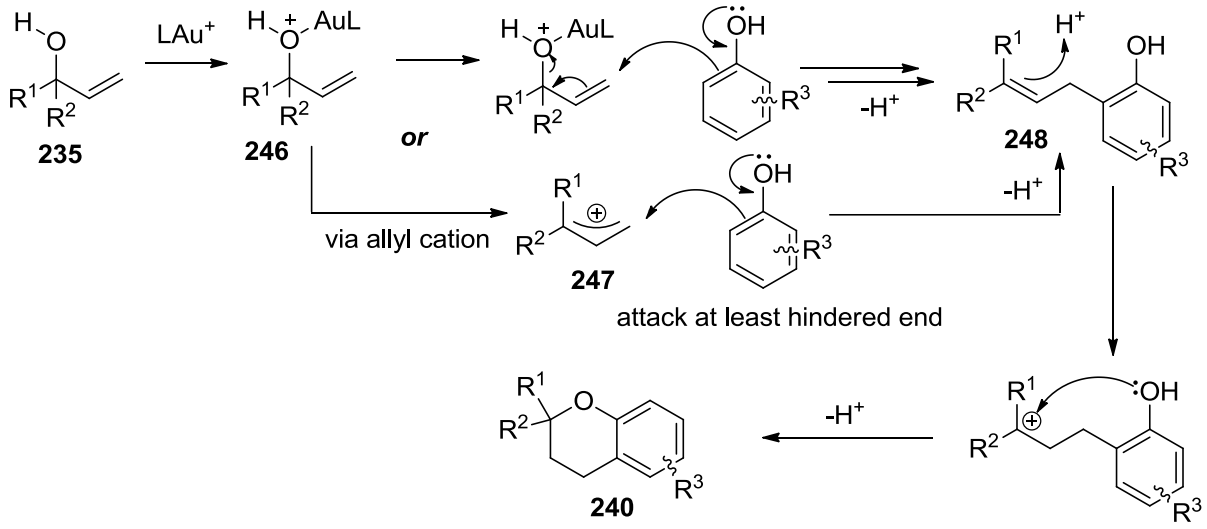
5.3.3 Gold(I)-catalysed chroman synthesis from allylic alcohols & phenols

As part of the nucleophile alcohol screen within the gold(I)-catalysed allylic etherification reaction, phenol was also shown to react (Table 5.7, entry 12). However, rather than yielding the expected allylic ether product, a chroman **240** was formed. This transformation was taken forward to be further developed, and to investigate the full scope of the reaction. After extensive optimisation of the reaction by Eloi Coutant, an Erasmus exchange student within the group, the most favourable conditions were found (Scheme 5.26).



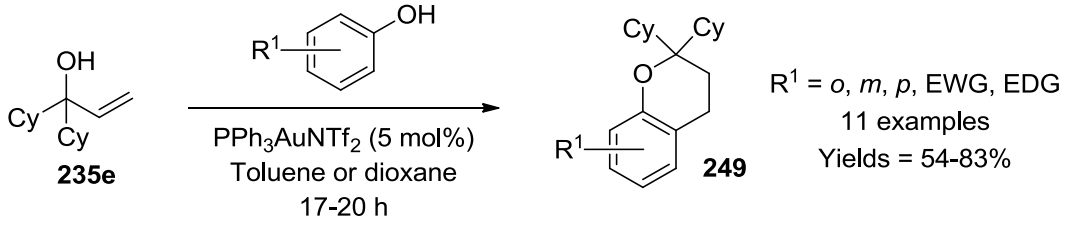
Scheme 5.26. Optimised conditions for the gold(I)-catalysed synthesis of chromans.

The reaction is thought to proceed *via* a Friedel-Crafts intermediate, followed by cyclisation to form the final desired chroman structure (Scheme 5.27).[43-46] There was evidence for this proposed mechanism when the reaction was carried out at lower temperatures, from which the Friedel-Crafts intermediate **248** could be isolated. The first step is the Friedel-Crafts allylation of the phenol *via* Markovnikov regioselectivity, resulting in **248**. This can occur through activation of the allylic alcohol through coordination of the oxygen atom to the gold(I) catalyst (**246**).[46, 47] The Friedel-Crafts allylation can take place through an S_N2'-type reaction (or S_N2-type reaction, depending on substitution patterns), or potentially through an allyl cation (**247**) to provide **248**. This is subsequently followed by acid-catalysed hydroalkoxylation to form the cyclised chroman **240**.[48]



Scheme 5.27. Proposed mechanism for the gold(I)-catalysed synthesis of chromans.

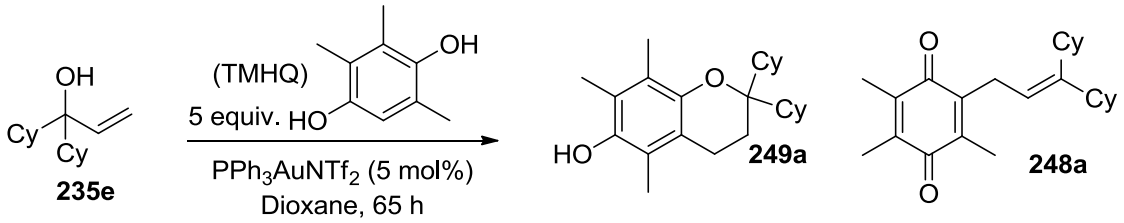
The reaction was shown by E. Coutant to be very general; being tolerant of many functional groups and differing substitutions around the phenol ring (Scheme 5.28). The author further extended the scope to TMHQ to further highlight the synthetic benefits of this reaction.



Scheme 5.28. Phenol nucleophile scope of the gold(I)-catalysed chroman synthesis.

TMHQ has been shown to be synthetically useful for the production of vitamin E and its derivatives.[35, 49] The general procedure of the optimised reaction had to be somewhat altered to enable the TMHQ to fully dissolve, hence dioxane was selected as the solvent. This reaction required further optimisation to achieve a good yield (Table 5.11).

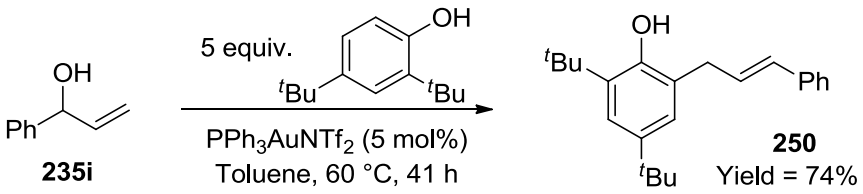
Table 5.11. Optimisation of the TMHQ nuclophile chroman synthesis.



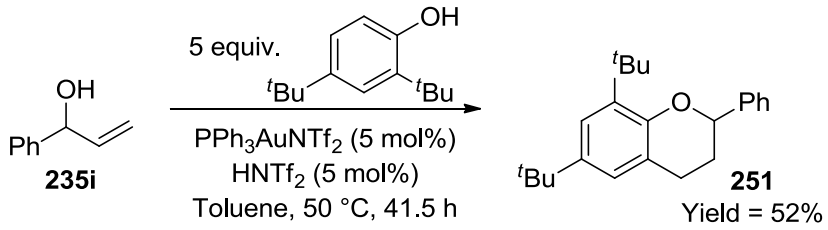
Entry	Temp. (°C)	Conditions	Product	Isolated Yield
1	80	Air	**249a** & **248a**	45% **249a** 35% **248a**
2	80	Argon	**249a**	69% **249a**
3	90	Argon, sealed tube	**249a**	83% **249a**

Under standard conditions, product **248a** was observed in 35% yield (entry 1). This can be attributed to the auto-oxidation of the TMHQ Friedel-Crafts intermediate. With product **248a** being formed, there was a poor yield of 45% of the desired product **249a**. When the reaction was carried out under an inert argon atmosphere (entry 2), product **248a** was not observed and **249a** was obtained in a good 69% yield. Finally, the reaction was performed in a sealed tube at a higher temperature of 90 °C (entry 3). This significantly improved the yield of **249a**, achieving a very good 83% yield.

During the allylic alcohol substrate screens,[50] it was observed that certain allylic alcohol substrates (for example the secondary allylic alcohol **235i**) would not undergo the cyclisation step to form the desired chroman product. Instead, the reaction ceased at the Friedel-Crafts allylation intermediate **250** with a 74% yield (Scheme 5.29). If the proposed cyclisation step from **250** to the desired chorman product is indeed acid-catalysed, as suggested in Scheme 5.27, the reaction could be forced to undergo cyclisation with the addition of a Brønsted acid co-catalyst. Pleasingly, the addition of a catalytic amount of $HNTf_2$ successfully provides the corresponding chroman **251**; suggesting that the cyclisation step is indeed acid-catalysed (Scheme 5.30).



Scheme 5.29. Standard gold(I)-catalysed conditions using **235i**.



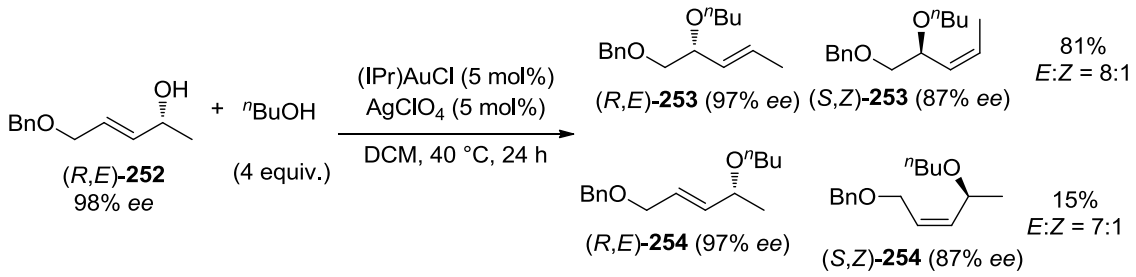
Scheme 5.30. Chroman synthesis using Brønsted acid co-catalyst.

5.4 Conclusions & Future Work

A novel gold(I)-catalysed allylic etherification procedure was developed, the reaction was shown to be mild, regio- and stereoselective. The method utilises completely unactivated starting materials, in form of allylic alcohols and nucleophile alcohols. The reaction was shown to be highly general, with excellent substrate scope; encompassing primary, secondary and tertiary alcohols. Due to the mild reaction conditions, many functional groups were tolerated, including alkyl chlorides, isolated alkenes, as well as both acid-sensitive and base-sensitive groups.[51]

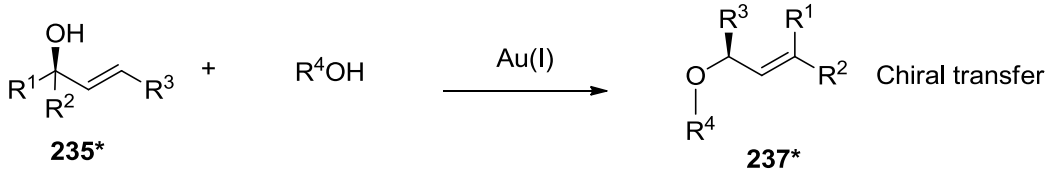
The mild reaction conditions were further improved with the use of novel gold(I) 1,2,3-triazolylidene catalysts. Using these catalysts, the number of equivalents of nucleophile alcohol was reduced from 5 equivalents to 1.1 equivalents. In addition to this, the transformation can now be performed at 25 °C, compared to 50 °C originally. Currently these updated conditions are only useful for reactions of tertiary allylic alcohols with primary alcohol nucleophiles. Future work in this area would be to attempt to extend this methodology to increase the substrate scope to include all forms of starting materials.[36]

The allylic etherification method was shown to have good selectivities, however it is desirable to investigate the potential for including asymmetric examples. Shortly after our own article was published,[51] a paper by Widenhoefer also reported a gold(I)-catalysed allylic etherification from unactivated starting materials.[52] This paper demonstrated that the reaction could be extended to include chiral transfer reactions; starting with enantiopure allylic alcohols (*R*,*E*)-**252** to yield enantiopure allylic ethers **253** & **254** (one example given, Scheme 5.31).

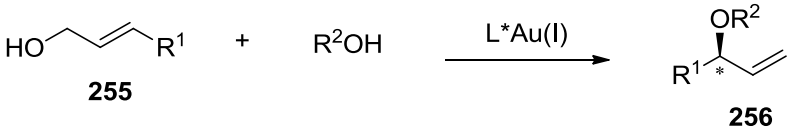


Scheme 5.31. Gold(I)-catalysed chiral transfer allylic etherification by Widenhoefer.

Future work in this area would be to fully determine the scope of chiral transfer reactions (Scheme 5.32). Investigations into the potential for catalytic enantioselective reactions would be additionally beneficial. This could be carried out by starting from racemic substrates **255**, and utilising a chiral gold(I) catalyst to achieve enantiopure products **256**.(Scheme 5.33). Further understanding of these transformations using computational investigations, in collaboration with Prof. S. A. Macgregor (Heriot-Watt University) is currently underway.



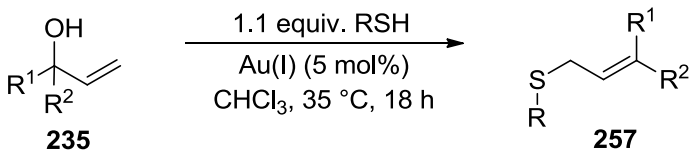
Scheme 5.32. Gold(I)-catalysed chiral transfer allylic etherification.



Scheme 5.33. Enantioselective gold(I)-catalysed allylic etherification.

An unexpected chroman product was obtained from the use of phenol as a nucleophile in the gold(I)-catalysed allylic etherification method. This reaction was further developed and was shown to be extremely useful in the synthesis of substituted chromans. Functional group tolerance was excellent, and the procedure was shown to have potential use in the production of vitamin E and its analogues.[53]

Using the allylic etherification method as a basis, work is currently underway to extend the scope of the reaction to sulfur nucleophiles (Scheme 5.34). The product of this gold(I)-catalysed reaction of allylic alcohols **235** with thiols or thiophenols, is allylic thioether **257**. The optimised conditions are mild and the reaction is tolerant of many functional groups and substitution patterns.



Scheme 5.34. Gold(I)-catalysed allylic thioetherification.

5.5 Experimental

General Experimental Section

^{1}H NMR spectra were recorded on Bruker AV 300 and AV 400 spectrometers at 300 and 400 MHz respectively and referenced to residual solvent. ^{13}C NMR spectra were recorded using the same spectrometers at 75 and 100 MHz respectively. Chemical shifts (δ in ppm) were referenced to tetramethylsilane (TMS) or to residual solvent peaks ($CDCl_3$ at δ_H 7.26). *J* values are given in Hz and s, d, dd, t, q, qn and m abbreviations correspond to singlet, doublet, doublet of doublet, triplet, quartet, quintet and multiplet. Mass spectra were obtained at the EPSRC National Mass Spectrometry Service Centre in Swansea. Infrared spectra were obtained on Perkin-Elmer Spectrum 100 FT-IR Universal ATR Sampling Accessory, deposited neat or as a chloroform solution to a diamond/ZnSe plate. Flash column chromatography was carried out using Matrix silica gel 60 from Fisher Chemicals and TLC was performed using Merck silica gel 60 F254 precoated sheets and visualised by UV (254 nm) or stained by the use of aqueous acidic $KMnO_4$ or aqueous acidic ceric ammonium molybdate as appropriate. Petrol ether refers to petroleum ether (40–60 °C). Dichloromethane (DCM) was purchased from Fisher and used without further purification. All alcohol nucleophiles were purchased from Sigma-Aldrich or Acros, and used without further purification. The gold(I)-catalysed reactions were carried out without the need for dry solvents or inert atmosphere, unless stated otherwise.

Allylic Alcohol Starting Materials:

Allylic alcohol **235d** was purchased from Sigma-Aldrich.

Allylic alcohols **235c, e-g** & **i** were obtained following known literature procedure with Grignard addition to ketones/aldehydes.[54] All characterisation was comparable to literature values; **235c**, **235f** & **235g**,[54] **235e**,[55] **235i**,[56].

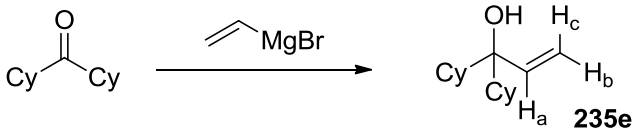
Grignard addition to ketone/aldehyde: Ketone/aldehyde (1 equiv.) was dissolved in dry THF. 1 M Vinylmagnesium chloride (1.2 equiv.) was added dropwise over 1.5 h at 0 °C, and left to react overnight at room temperature under an atmosphere for N_2. The reaction was then quenched with saturated ammonium chloride solution. The product was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The product was purified using flash column chromatography.

3,4,4-Trimethylpent-1-en-3-ol **235c**:[54]

235c

The desired product was obtained as a colourless oil (0.64 g, 4.99 mmol, 25%). ν_{max}/cm^{-1} 3500-3200 br w (O-H), 2969 m 2876 w (C-H), 1642 w (C=C), ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.07 (dd, *J* = 17.3, 10.9 Hz, 1H, H_a), 5.21 (dd, *J* = 17.3, 1.5 Hz, 1H, H_c), 5.07 (dd, *J* = 10.9, 1.5 Hz, 1H, H_b), 1.38 (s, 1H, OH), 1.23 (s, 3H, $CC\underline{H_3}$), 0.93 (s, 9H, $C(C\underline{H_3})_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4 (CH), 112.4 (CH_2), 77.4 (C), 37.3 (C), 25.4 (CH_3), 23.4 (CH_3).

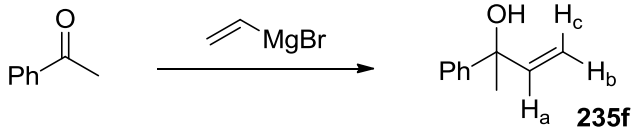
1,1-Dicyclohexylprop-2-en-1-ol **235e**:[55]



235e

The desired product was obtained as a colourless oil (0.78 g, 3.51 mmol, 69%). ν_{max}/cm^{-1} 3500-3400 w (O-H), 2921 s 2850 s (C-H), 1637 w (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (dd, *J* = 17.2, 11.1 Hz, 1H, H_a), 5.15 (dd, *J* = 11.1, 1.7 Hz, 1H, H_b), 5.12 (dd, *J* = 17.2, 1.7 Hz, 1H, H_c), 1.85 – 1.45 (m, 11H, alkyl CH_2 + CH), 1.28 (s, 1H, O<u>H</u>), 1.27 – 0.85 (m, 11H, alkyl CH_2 + CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.7 (CH), 113.3 (CH_2), 79.4 (C), 42.8 (CH), 27.4 (CH_2), 27.0 (CH_2), 26.8 (CH_2), 26.7 (CH_2), 26.2 (CH_2).

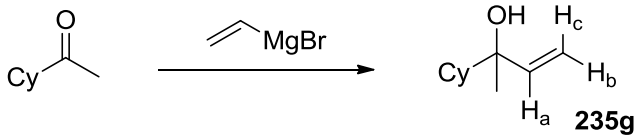
2-Phenylbut-3-en-2-ol **235f**:[54]



235f

Product isolated after flash column chromatography was contaminated with self-aldol product. To remove this, the mixture was stirred overnight in 3 M sodium hydroxide solution. The desired product was obtained as a yellow oil (1.38 g, 9.31 mmol, 58%). ν_{max}/cm^{-1} 3500-3100 m (O-H), 3087 w 3060 w 3028 w 2980 m 2929 w (C-H), 1640 w (C=C), 1492 m 1446 m 1410 m (aromatic C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 – 7.23 (m, 5H, Ar-H), 6.18 (dd, *J* = 17.3, 10.6 Hz, 1H, H_a), 5.31 (dd, *J* = 17.3, 1.1 Hz, 1H, H_c), 5.16 (dd, *J* = 10.6, 1.1 Hz, 1H, H_b), 1.95 (s, 1H, O<u>H</u>), 1.67 (s, 3H, C<u>H_3</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.5 (C), 144.9 (CH), 128.4 (CH), 127.1 (CH), 125.3 (CH), 112.5 (CH_2), 74.9 (C), 29.4 (CH_3).

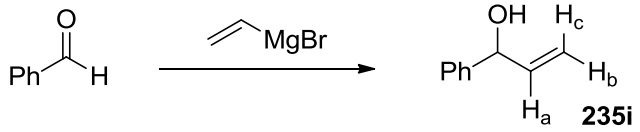
2-Cyclohexylbut-3-en-2-ol **235g**:[54]



235g

Product isolated after flash column chromatography was contaminated with self-aldol product. To remove this, the mixture was stirred overnight in 3 M sodium hydroxide solution. The desired product was obtained as a yellow oil (1.16 g, 7.52 mmol, 38%). ν_{max}/cm^{-1} 3500-3100 m (O-H), 2924 s 2853 s (C-H), 1642 w (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (dd, *J* = 17.4, 10.8 Hz, 1H, H_a), 5.18 (dd, *J* = 17.4, 1.4 Hz, 1H, H_c), 5.06 (dd, *J* = 10.8, 1.4 Hz, 1H, H_b), 1.86 – 1.59 (m, 5H, alkyl CH_2 + CH), 1.41 (s, 1H, O<u>H</u>), 1.23 (s, 3H, C<u>H</u>$_3$), 1.40 – 0.91 (m, 6H, alkyl CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5 (CH), 112.0 (CH_2), 75.4 (C), 48.1 (CH), 27.6 (CH_2), 27.2 (CH_2), 26.8 (CH_2), 26.7 (CH_2), 26.6 (CH_2), 25.3 (CH_3).

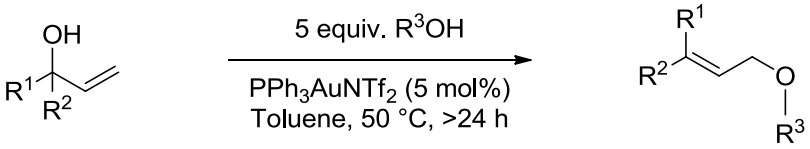
1-Phenylprop-2-en-1-ol **235i**:[57]



235i

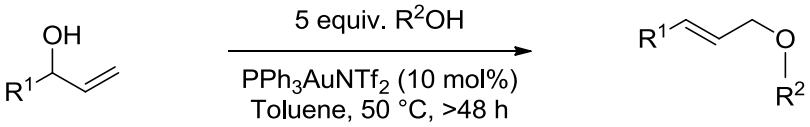
The product was obtained as a colourless oil (2.67 g, 19.9 mmol, 70%).ν_{max}/cm^{-1} 3500-3300 br m (O-H), 3063 w (C-H), 1642 w (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.20 (m, 5H, Ar-H), 6.16 – 5.98 (m, 1H, H_a), 5.36 (d, *J* = 17.1 Hz, 1H, H_c), 5.24 – 5.17 (m, 2H, H_b + PhC<u>H</u>), 2.01 (d, *J* = 3.8 Hz, 1H, O<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7 (C), 140.3 (CH), 128.7 (CH), 127.9 (CH), 126.5 (CH), 115.3 (CH_2), 75.5 (CH).

A: General Synthetic Procedure for Tertiary Allylic Alcohol Substrates:



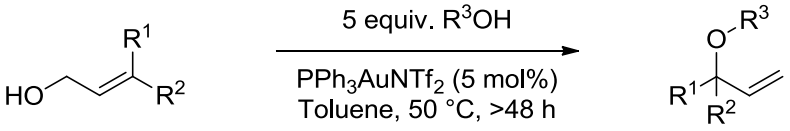
The gold-catalysed reactions were all carried out in 1 dram screw-cap vials. To a toluene solution (0.386 M) of allylic alcohol (1 equiv.) and alcohol nucleophile (5 equiv.), PPh_3AuNTf_2 (as a 2:1 toluene adduct) (5 mol%) was added. The reaction mixture was allowed to stir at 50 °C for over 24 hours. The reaction was then filtered through a plug of silica (40:1 petroleum ether:diethyl ether). The filtrate was concentrated under reduced pressure, and a crude ^{1}H NMR was obtained to determine S_N2':S_N2 and *E*:*Z* ratios. The crude material was purified by flash column chromatography.

B: General Synthetic Procedure for Secondary Allylic Alcohol Substrates:



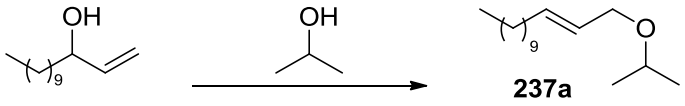
The gold-catalysed reactions were all carried out in 1 dram screw-cap vials. To a toluene solution (0.386 M) of allylic alcohol (1 equiv.) and alcohol nucleophile (5 equiv.), PPh_3AuNTf_2 (as a 2:1 toluene adduct) (10 mol%) was added. The reaction mixture was allowed to stir at 50 °C for over 48 hours. The reaction was then filtered through a plug of silica (40:1 petroleum ether:diethyl ether). The filtrate was concentrated under reduced pressure, and a crude ^{1}H NMR was obtained to determine S_N2':S_N2 and *E*:*Z* ratios. The crude material was purified by flash column chromatography.

C: General Synthetic Procedure for Primary Allylic Alcohol Substrates:



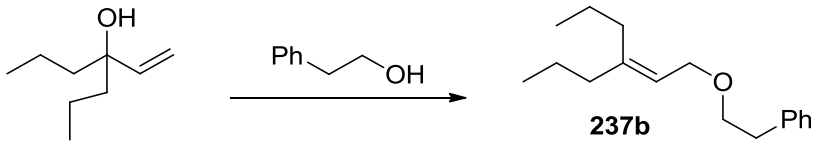
As for **A**, but reaction time was >48 h instead of >24 h.

(*E*)-1-*iso*Propoxypent-2-ene **237a**:



Analysis of crude reaction mixture showed that *E*:*Z* ratio was 8:1, with S_N2':S_N2 ratio of 11:1. Purified by flash column chromatography with silver nitrate impregnated silica; using petroleum ether as an eluent. Product obtained as a colourless oil in 13:1 *E*:*Z* ratio, with S_N2':S_N2 ratio of >20:1 (22.5 mg, 0.094 mmol, 91%). ν_{max}/cm^{-1} 2918 s 2852 s (C-H), 1684 m (C=C), 1453 m 1372 m (C-H bending), 1090 s (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76 – 5.46 (m, 2H, C<u>H</u>=C<u>H</u>), 3.90 (d, *J* = 6.0 Hz, 2H, OC<u>H</u>$_2$), 3.61 (hept, *J* = 6.1 Hz, 1H, OC<u>H</u>$(CH_3)_2$), 2.03 (q, *J* = 6.7 Hz, 2H, CHC<u>H</u>$_2$$CH_2$), 1.41 – 1.21 (m, 16H, alkyl CH_2), 1.16 (d, *J* = 6.1 Hz, 6H, OCH$(C\underline{H}_3)_2$), 0.93 – 0.83 (m, 3H, $CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.4 (CH), 126.9 (CH), 70.7 (CH), 69.1 (CH_2), 32.5 (CH_2), 32.1 (CH_2), 29.8 (CH_2 x 2), 29.7 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 22.9 (CH_2), 22.3 (CH_3), 14.3 (CH_3). Found (APCI) $[M+NH_4]^+$ 258.2794, $C_{16}H_{36}NO$ requires 258.2791.

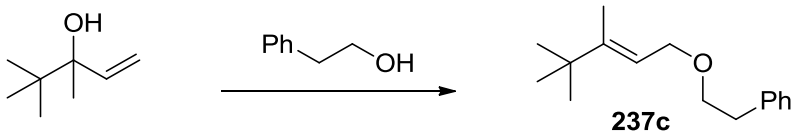
(2-((3-Propylhex-2-en-1-yl)oxy)ethyl)benzene **237b**:



237b

Purified using flash column chromatography with silver nitrate impregnated silica; using a gradient eluent system of neat petroleum ether → 50:1 petroleum ether:diethyl ether. Product obtained as a colourless oil (19.8 mg, 0.080 mmol, 78%). ν_{max}/cm^{-1} 2959 m 2931 m 2871 m (C-H), 1662 w (C=C), 1605 w 1497 w 1455 m (aromatic C=C), 1093 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.17 (m, 5H, aromatic CH), 5.34 (t, *J* = 6.7 Hz, 1H, $OCH_2C\underline{H}$), 4.02 (d, *J* = 6.7 Hz, 2H, $OC\underline{H_2}CH$), 3.64 (t, *J* = 7.4 Hz, 2H, $OC\underline{H_2}CH_2$), 2.91 (t, *J* = 7.4 Hz, 2H, $OCH_2C\underline{H_2}$), 2.07 – 1.93 (m, 4H, $=CC\underline{H_2}CH_2$), 1.51 – 1.30 (m, 4H, $=CCH_2C\underline{H_2}$), 0.89 (t, *J* = 7.3 Hz, 3H, $CH_2C\underline{H_3}$), 0.88 (t, *J* = 7.3 Hz, 3H, $CH_2C\underline{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3 (C), 139.2 (C), 129.0 (CH), 128.5 (CH), 126.3 (CH), 121.4 (CH), 71.2 (CH_2), 67.4 (CH_2), 39.1 (CH_2), 36.6 (CH_2), 32.8 (CH_2), 21.9 (CH_2), 21.2 (CH_2), 14.3 (CH_3), 14.1 (CH_3). Found (ESI) $[M+NH_4]^+$ 264.2326, $C_{17}H_{30}NO$ requires 264.2322.

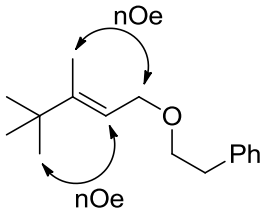
(*E*)-(2-((3,4,4-Trimethylpent-2-en-1-yl)oxy)ethyl)benzene **237c**:



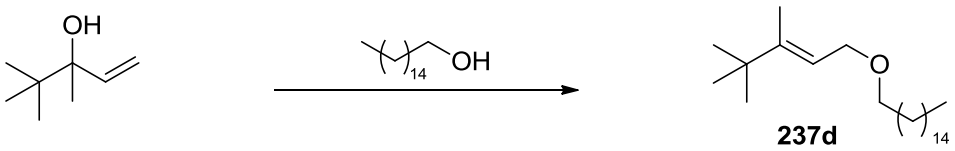
237c

Purified using flash column chromatography; using a gradient eluent system of neat hexane → 50:1 hexane:diethyl ether. Product obtained as a colourless oil (16.7 mg, 0.072 mmol, 76%). ν_{max}/cm^{-1} 3028 w 2963 m 2867 m (C-H), 1657 w (C=C), 1605 w 1497 m 1454 m (aromatic C=C), 1105 s (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.18 (m, 5H, aromatic CH), 5.39 (tq, *J* = 6.2, 1.1 Hz, 1H, $OCH_2C\underline{H}$), 4.05 (d, *J* = 6.2 Hz, 2H, $OC\underline{H_2}CH$), 3.65 (t, *J* = 7.4 Hz, 2H, $OC\underline{H_2}CH_2$), 2.92 (t, *J* = 7.4 Hz, 2H, $OCH_2C\underline{H_2}$), 1.64 (d, *J* = 1.1 Hz, 3H, $CH{=}CC\underline{H_3}$), 1.06 (s, 9H, $C(C\underline{H_3})_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.2 (C), 139.2 (C), 129.0 (CH), 128.5 (CH), 126.3 (CH), 118.2 (CH), 71.4 (CH_2), 68.4 (CH_2), 36.6 (CH_2), 36.4 (C), 29.0 (CH_3), 13.2 (CH_3). Found (APCI) $[M+H]^+$ 233.1899, $C_{16}H_{25}O$ requires 233.1900.

2D NOESY confirms *E*-isomer:

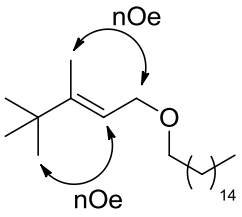


(*E*)-1-((3,4,4-Trimethylpent-2-en-1-yl)oxy)hexadecane **237d**:

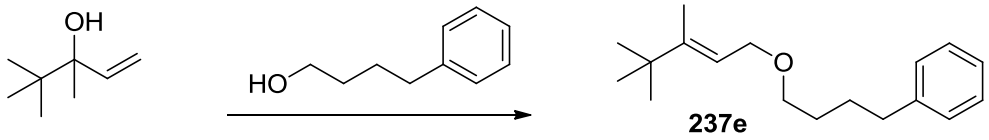


Purified using flash column chromatography; using a gradient eluent system of neat petroleum ether → 80:1 petroleum ether:diethyl ether. Product obtained as a colourless oil (33.7 mg, 0.096 mmol, 83%). ν_{max}/cm^{-1} 2955 s 2852 s (C-H), 1651 w (C=C), 1465 m 1360 m (C-H bending), 1106 s (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39 (tq, *J* = 6.2, 1.2 Hz, 1H, $OCH_2C\underline{H}$), 4.00 (d, *J* = 6.2, 2H, $OC\underline{H_2}CH$), 3.41 (t, *J* = 6.8 Hz, 2H, $OC\underline{H_2}CH_2$), 1.64 (d, *J* = 1.2 Hz, 3H, $CH=C(C\underline{H_3})$), 1.25 (s, 28H, alkyl CH_2), 1.05 (s, 9H, $C(C\underline{H_3})_3$), 0.91 – 0.85 (m, 3H, $CH_2C\underline{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.8 (C), 118.5 (CH), 70.7 (CH_2), 68.3 (CH_2), 36.4 (C), 32.1 (CH_2), 30.0 (CH_2), 29.9 (CH_3), 29.82 (3 × CH_2 overlapping peaks), 29.77 (2 × CH_2 overlapping peaks), 29.7 (CH_2), 29.5 (CH_2), 29.0 (3 × CH_2 overlapping peaks), 26.4 (CH_2), 22.9 (CH_2), 14.9 (CH_3), 13.2 (CH_3). Found (ESI) $[M+NH_4]^+$ 370.4048, $C_{24}H_{52}NO$ requires 370.4043.

2D NOESY confirms *E*-isomer is major isomer:



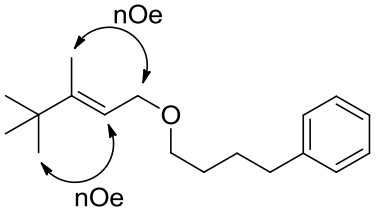
(*E*)-(4-((3,4,4-Trimethylpent-2-en-1-yl)oxy)butyl)benzene **237e**:



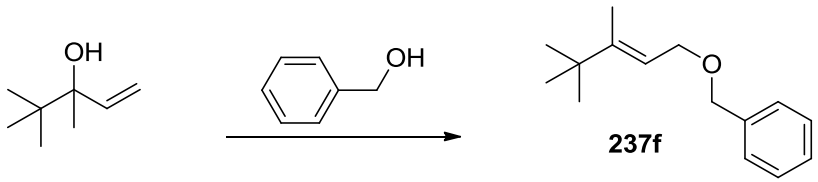
237e

Analysis of crude reaction mixture showed that S_N2':S_N2 ratio was 12:1. Purified using flash column chromatography; using a gradient eluent system of neat hexane → 20:1 hexane:diethyl ether. Product obtained as a colourless oil with S_N2':S_N2 ratio of 15:1 (23.3 mg, 0.089 mmol, 75%). ν_{max}/cm^{-1} 3027 w 2954 m 2937 m 2862 m (C-H), 1655 w (C=C), 1604 w 1496 m 1453 m (aromatic C=C), 1107 s (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.15 (m, 5H, aromatic CH), 5.39 (tq, *J* = 6.2, 1.2 Hz, 1H, $OCH_2C\underline{H}$), 4.00 (d, *J* = 6.2 Hz, 2H, $OC\underline{H_2}CH$), 3.45 (t, *J* = 6.4 Hz, 2H, $OC\underline{H_2}CH_2$), 2.65 (t, *J* = 7.4 Hz, 2H, $CH_2C\underline{H_2}Ph$), 1.77 – 1.58 (m, 7H, alkyl $C\underline{H_2}$ & $C(C\underline{H_3})$), 1.06 (s, 9H, $C(C\underline{H_3})_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0 (C), 142.6 (C), 128.6 (CH), 128.4 (CH), 125.8 (CH), 118.4 (CH), 70.4 (CH_2), 68.3 (CH_2), 36.4 (C), 35.9 (CH_2), 29.6 (CH_2), 29.0 (CH_3), 28.3 (CH_2), 13.2 (CH_3). Found (EI) $[M]^+$ 260.2136, $C_{18}H_{28}O$ requires 260.2135.

2D NOESY confirms *E*-isomer:

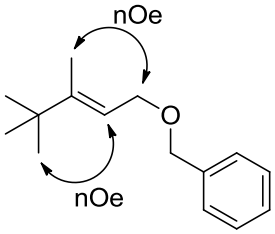


(*E*)-(((3,4,4-Trimethylpent-2-en-1-yl)oxy)methyl)benzene **237f**:

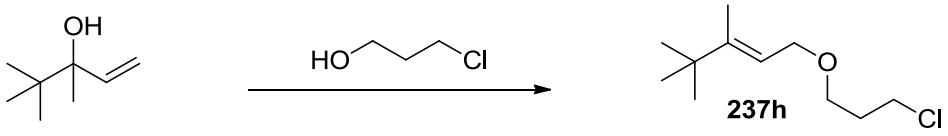


Purified using flash column chromatography; using a gradient eluent system of neat hexane → 50:1 hexane:diethyl ether. Product obtained as a colourless oil (19.9 mg, 0.091 mmol, 77%). ν_{max}/cm^{-1} 2964 s 2867 m (C-H), 1655 w (C=C), 1496 w 1454 m 1360 s (aromatic C=C), 1101 s (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 5H, aromatic CH), 5.45 (tq, *J* = 6.3, 1.2 Hz, 1H, $OCH_2C\underline{H}$), 4.52 (s, 2H, $OC\underline{H_2}Ar$), 4.06 (dq, *J* = 6.3, 0.7 Hz, 2H, $OC\underline{H_2}CH$), 1.65 – 1.62 (m, 3H, $CHCC\underline{H_3}$), 1.06 (s, 9H, $C(C\underline{H_3})_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6 (C), 138.7 (C), 128.5 (CH), 128.0 (CH), 127.7 (CH), 118.1 (CH), 72.4 (CH_2), 67.6 (CH_2), 36.4 (C), 29.0 (CH_3), 13.2 (CH_3). Found (APCI) $[M+NH_4]^+$ 236.2007, $C_{15}H_{26}NO$ requires 236.2009.

2D NOESY confirms *E*-isomer:

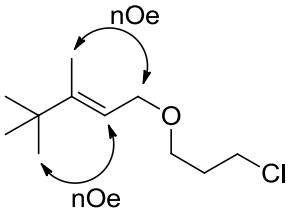


(*E*)-1-(3-Chloropropoxy)-3,4,4-trimethylpent-2-ene **237h**:

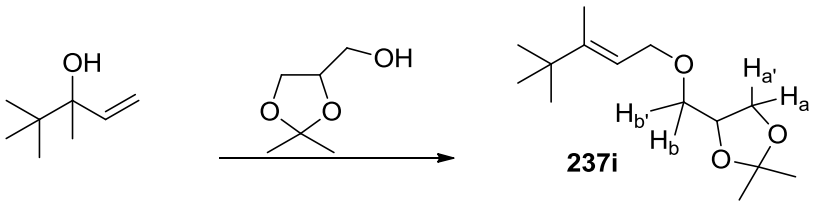


Purified using flash column chromatography; using a gradient eluent system of neat petroleum ether → 50:1 petroleum ether:diethyl ether. Product obtained as a colourless oil (15.5 mg, 0.076 mmol, 65%). ν_{max}/cm^{-1} 2971 s 2902 s (C-H), 1656 w (C=C), 1452 m 1406 m 1394 m 1381 m (C-H bending), 1066 s 1057 s (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37 (tq, *J* = 6.2, 1.2 Hz, 1H, $OCH_2C\underline{H}$), 4.02 (d, *J* = 6.2 Hz, 2H, $OC\underline{H_2}CH$), 3.65 (t, *J* = 6.5 Hz, 2H, $OC\underline{H_2}CH_2$), 3.56 (t, *J* = 5.9 Hz, 2H, $CH_2C\underline{H_2}Cl$), 2.03 (app. p, *J* = 6.2 Hz, 2H, $CH_2C\underline{H_2}CH_2$), 1.66 – 1.63 (m, 3H, $CH=C(C\underline{H_3})$), 1.05 (s, 9H, $C(C\underline{H_3})_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.5 (C), 118.0 (CH), 68.41 (CH_2), 66.6 (CH_2), 42.3 (CH_2), 36.4 (C), 32.9 (CH_2), 29.0 (CH_3), 13.2 (CH_3). Found (APCI) $[M+H]^+$ 205.1356, $C_{11}H_{22}ClO$ requires 205.1354.

2D NOESY confirms *E*-isomer:

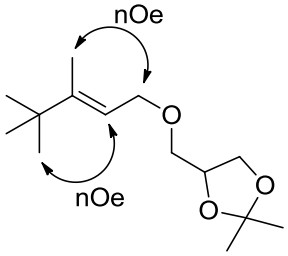


(*E*)-2,2-Dimethyl-4-(((3,4,4-trimethylpent-2-en-1-yl)oxy)methyl)-1,3-dioxolane **227i**:

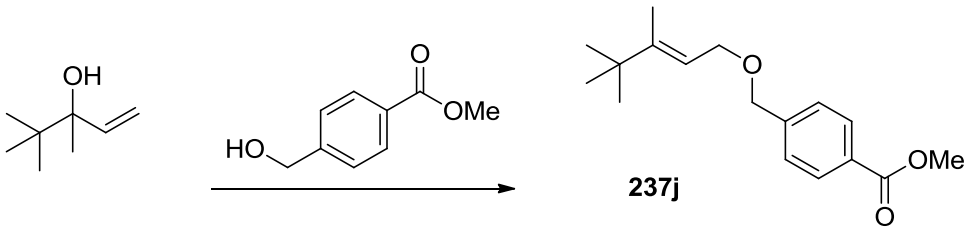


Purified using flash column chromatography; using a gradient eluent system of neat hexane → 40:1 hexane:diethyl ether. Product obtained as a colourless oil (22.0 mg, 0.091 mmol, 77%). ν_{max}/cm^{-1} 2965 s 2870 s (C-H), 1655 w (C=C), 1456 m 1370 s (C-H bending), 1068 s 1054 s (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38 (tq, *J* = 6.2, 1.2 Hz, 1H, $OCH_2C\underline{H}$=C), 4.29 (app. qn, *J* = 6.3 Hz, 1H, $OC\underline{H}CH_2O$), 4.10 – 4.04 (m, 3H, $OC\underline{H_2}CH$=C & $H_a/H_{a'}$), 3.72 (dd, *J* = 8.3, 6.4 Hz, 1H, $H_a/H_{a'}$), 3.52 (dd, *J* = 9.8, 5.9 Hz, 1H, $H_b/H_{b'}$), 3.42 (dd, *J* = 9.8, 5.6 Hz, 1H, $H_b/H_{b'}$), 1.64 (d, *J* = 1.2 Hz, 3H, CH=C($C\underline{H_3}$)), 1.42 (s, 3H, OC($C\underline{H_3}$)$_2$O), 1.36 (s, 3H, OC($C\underline{H_3}$)$_2$O), 1.04 (s, 9H, CH=C($C\underline{H_3}$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.5 (C), 117.9 (CH), 109.5 (C), 74.9 (CH), 71.4 (CH_2), 69.0 (CH_2), 67.2 (CH_2), 36.4 (C), 29.0 (CH_3), 27.0 (CH_3), 25.5 (CH_3), 13.2 (CH_3). Found (ESI) $[M+H]^+$ 243.1960, $C_{14}H_{27}O_3$ requires 243.1955.

2D NOESY confirms *E*-isomer:

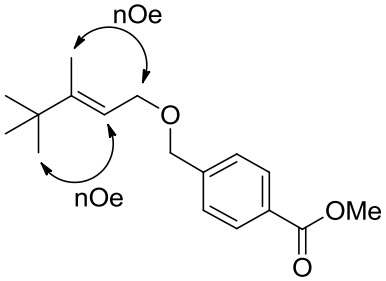


(*E*)-Methyl 4-(((3,4,4-trimethylpent-2-en-1-yl)oxy)methyl)benzoate **237j**:

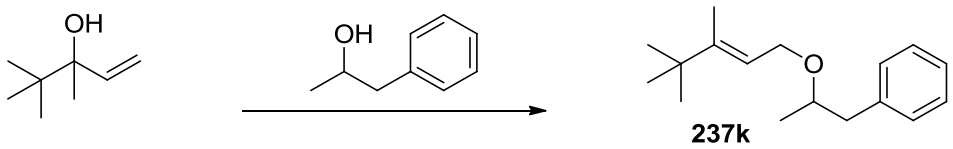


Purified using flash column chromatography; using a gradient eluent system of neat hexane → 10:1 hexane:diethyl ether. Product obtained as a colourless oil (23.9 mg, 0.086 mmol, 74%). ν_{max}/cm^{-1} 2954 m 2868 m (C-H), 1722 s (C=O), 1658 w (C=C), 1613 m, 1578 w 1435 m (aromatic C=C), 1275 s 1105 s (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.42 (d, *J* = 8.0 Hz, 2H, Ar-H), 5.44 (tq, *J* = 6.3, 1.2 Hz, 1H, $OCH_2C\underline{H}$), 4.56 (s, 2H, $OC\underline{H_2}Ar$), 4.07 (d, *J* = 6.3 Hz, 2H, $OC\underline{H_2}CH$), 3.91 (s, 3H, $OC\underline{H_3}$), 1.63 (d, 3H, *J* = 1.2 Hz, $CH=C(C\underline{H_3})$), 1.05 (s, 9H, $C(C\underline{H_3})_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1 (C), 148.0 (C), 144.1 (C), 129.8 (CH), 129.4 (C), 127.5 (CH), 117.7 (CH), 71.7 (CH_2), 67.9 (CH_2), 52.2 (CH_3), 36.4 (C), 29.0 (CH_3), 13.2 (CH_3). Found (ESI) $[M+NH_4]^+$ 294.2069, $C_{17}H_{28}NO_3$ requires 294.2064.

2D NOESY confirms *E*-isomer:



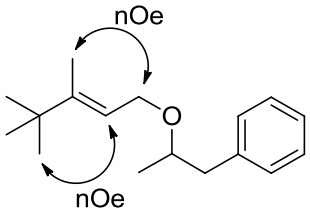
(*E*)-(2-((3,4,4-Trimethylpent-2-en-1-yl)oxy)propyl)benzene **237k**:



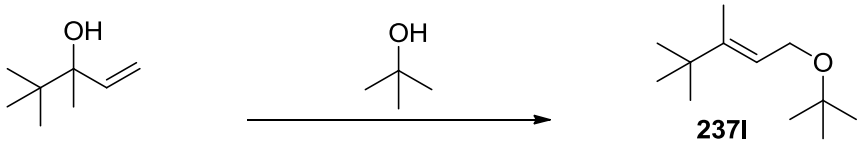
237k

Purified using flash column chromatography; using a gradient eluent system of neat petroleum ether → 50:1 petroleum ether:diethyl ether. Product obtained as a colourless oil (20.7 mg, 0.084 mmol, 71%). ν_{max}/cm^{-1} 3028 w 2965 s 2867 m (C-H), 1656 w (C=C), 1604 w 1496 m 1453 m (aromatic C=C), 1096 s (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33 (tq, *J* = 6.2, 1.2 Hz, 1H, $OCH_2C\underline{H}$), 4.06 (dd, *J* = 12.0, 6.2 Hz, 1H, $OC\underline{H}H'CH$), 3.99 (dd, *J* = 12.0, 6.2 Hz, 1H, $OCH\underline{H}'CH$), 3.64 (dp, *J* = 6.8, 6.1 Hz, 1H, $OC\underline{H}$), 2.96 (dd, *J* = 13.4, 6.1 Hz, 1H, $PhC\underline{H}H'CH$), 2.63 (dd, *J* = 13.4, 6.8 Hz, 1H, $PhCH\underline{H}'CH$), 1.60 (d, *J* = 1.2 Hz, 3H, $CH=C(C\underline{H}_3)$), 1.15 (d, *J* = 6.1 Hz, 3H, $OCHC\underline{H}_3$), 1.03 (s, 9H, $C(C\underline{H}_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7 (C), 139.4 (C), 129.6 (CH), 128.3 (CH), 126.1 (CH), 118.7 (CH), 76.1 (CH), 66.1 (CH_2), 43.3 (CH_2), 36.3 (C), 29.0 (CH_3), 19.8 (CH_3), 13.2 (CH_3). Found (APCI) $[M+H]^+$ 247.2054, $C_{17}H_{27}O$ requires 247.2056.

2D NOESY confirms *E*-isomer is major isomer:



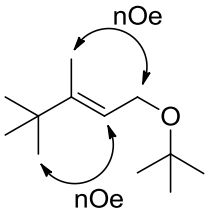
(*E*)-1-(*tert*-Butoxy)-3,4,4-trimethylpent-2-ene **237l**:



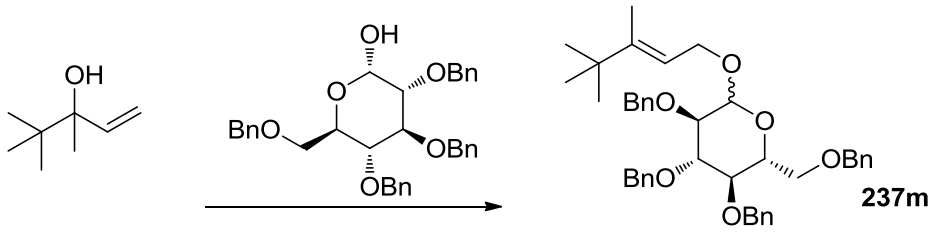
237l

Purified using flash column chromatography; using a gradient eluent system of neat petroleum ether → 80:1 petroleum ether:diethyl ether. Product obtained as a colourless oil (12.6 mg, 0.068 mmol, 57%). ν_{max}/cm^{-1} 2966 s 2928 m 2869 m (C-H), 1659 w (C=C), 1464 m 1388 m 1361 s (C-H bending), 1055 s (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.33 (tq, *J* = 5.9, 1.1 Hz, 1H, $OCH_2C\underline{H}$), 3.96 (d, *J* = 5.9 Hz, 2H, $OC\underline{H_2}CH$), 1.62 (d, *J* = 1.1 Hz, 3H, $CC\underline{H_3}$), 1.23 (s, 9H, $OC(C\underline{H_3})_3$), 1.04 (s, 9H, $C(C\underline{H_3})_3$)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.2 (C), 119.8 (CH), 73.0 (C), 59.8 (CH_2), 36.3 (C), 29.0 (CH_3), 27.8 (CH_3), 13.2 (CH_3). Found (APCI) $[M-H]^+$ 183.1742, $C_{12}H_{23}O$ requires 183.1743.

2D NOESY confirms *E*-isomer is major isomer:



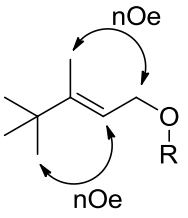
(2*R*,3*R*,4*S*,5*R*)-3,4,5-Tris(benzyloxy)-2-((benzyloxy)methyl)-6-(((*E*)-3,4,4-trimethylpent-2-en-1-yl)oxy)tetrahydro-2*H*-pyran **237m**:



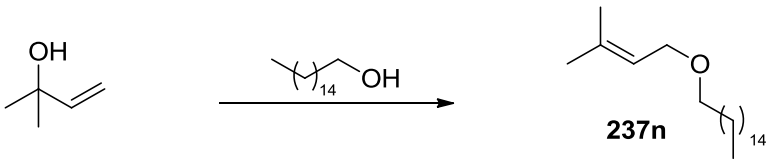
For solubility reasons, chloroform was used instead of toluene for this reaction. Purified using flash column chromatography; using a gradient eluent system of neat petroleum ether → 2:1 petroleum ether:diethyl ether. Product obtained as a colourless oil as a mixture of anomers with α:β ratio of ≈ 3:1 (39.1 mg, 0.060 mmol, 52%). ν_{max}/cm^{-1} 2959 w 2913 w 2866 w (C-H), 1694 w (C=C), 1605 w 1496 w 1453 m (aromatic C=C), 1084 s 1069 s (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.15 (m, 20H+20H', α & β aromatic CH), 5.54 – 5.48 (m, 1H', β-$OCH_2C\underline{H}$), 5.50 – 5.45 (m, 1H, α-$OCH_2C\underline{H}$), 5.09 – 3.48 (m, 17H+17H', α & β benzyl CH_2 & alkyl CH), 1.70 (d, *J* = 1.9 Hz, 3H', β-$CC\underline{H_3}$), 1.69 (d, *J* = 1.8 Hz, 3H, α-$CC\underline{H_3}$), 1.10 (d, *J* = 0.6 Hz, 9H+9H', α & β $C(C\underline{H_3})_3$); only major α-anomer characterised by ^{13}C NMR; ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.2 (C), 139.2 (C), 138.42 (C), 138.36 (C), 138.1 (C), 128.54 (CH), 128.50 (CH), 128.49 (CH), 128.47 (CH), 128.2 (CH), 128.10 (CH), 128.06 (CH), 128.0 (CH), 127.94 (CH), 127.87 (CH), 127.8 (CH), 127.7 (CH), 117.3 (CH), 95.4 (CH), 82.4 (CH), 79.8 (CH), 78.0 (CH), 75.9 (CH_2), 75.2 (CH_2), 73.6 (CH_2), 73.1 (CH_2), 70.3 (CH), 68.7 (CH_2), 64.3 (CH_2), 36.5 (C), 29.1 (CH_3), 13.2 (CH_3). Found (ESI) $[M+NH_4]^+$ 668.3944, $C42H_{54}NO_6$ requires 668.3946.

α & β Anomer ratio determined with assistance from 2D NMR work (C-H correlation); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89 (d, *J* = 4.9 Hz, 4H, α-OC<u>H</u>O), 4.48 (d, *J* = 7.8 Hz, 1H, β-OC<u>H</u>O).

2D NOESY confirms *E*-isomer is major isomer (both α & β anomers):

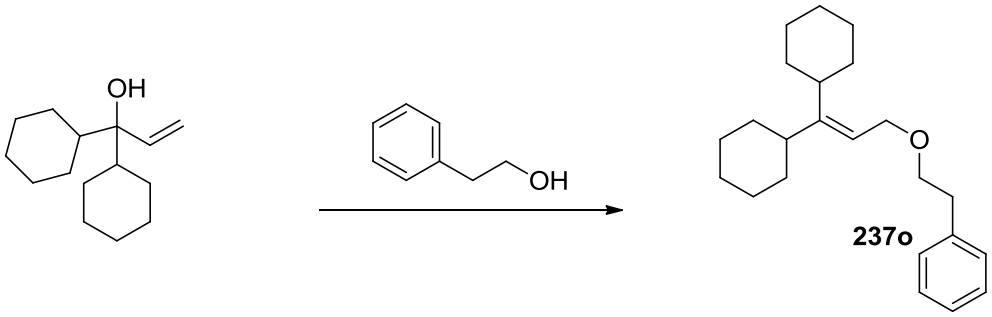


1-((3-Methylbut-2-en-1-yl)oxy)hexadecane **237n**:



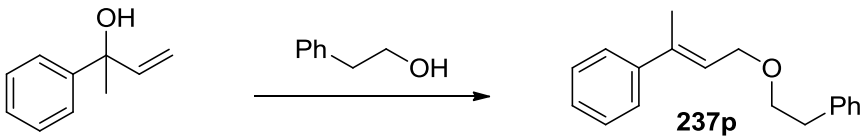
Analysis of crude reaction mixture showed that S_N2':S_N2 ratio was 5:1. Purified using flash column chromatography; using a gradient eluent system of neat hexane → 25:1 hexane:diethyl ether. Product obtained as a colourless oil with S_N2':S_N2 ratio of 6.5:1 (33.1 mg, 0.107 mmol, 62%). ν_{max}/cm^{-1} 2922 s 2853 s (C-H), 1675 w (C=C), 1466 m 1377 m (C-H bending), 1089 m (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.36 (tsept, *J* = 6.9, 1.4 Hz, 1H, $OCH_2C\underline{H}$), 3.93 (d, *J* = 6.9 Hz, 2H, $OC\underline{H_2}CH$), 3.39 (t, *J* = 6.7 Hz, 2H, $OC\underline{H_2}CH_2$), 1.74 (app. s, 3H, $C(C\underline{H_3})_2$), 1.67 (app. s, 3H, $C(C\underline{H_3})_2$), 1.38-1.16 (m, 28H, alkyl CH_2), 0.91 – 0.83 (m, 3H, $CH_2C\underline{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.7 (C), 121.5 (CH), 70.6 (CH_2), 67.4 (CH_2), 32.1 (CH_2), 30.0 (CH_2 overlapping signals), 29.9 (CH_2), 29.82 (CH_2), 29.77 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 26.4 (CH_2), 26.0 (CH_3), 22.9 (CH_2), 18.2 (CH_3), 14.3 (CH_3). Found (APCI) $[M+NH_4]^+$ 328.3567, $C_{21}H_{46}NO$ requires 328.3574.

(3-Phenethoxyprop-1-ene-1,1-diyl)dicyclohexane **237o**:



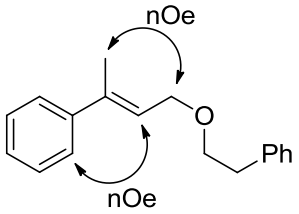
Purified using flash column chromatography; using a gradient eluent system of neat petroleum ether → 50:1 petroleum ether:diethyl ether. Product obtained as a colourless oil (20.1 mg, 0.062 mmol, 91%). ν_{max}/cm^{-1} 2988 s 2922 s (C-H), 1653 w (C=C), 1495 m 1449 m (aromatic C=C), 1057 s (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.13 (m, 5H, aromatic CH), 5.26 (t, *J* = 6.5 Hz, 1H, $OCH_2C\underline{H}$), 4.09 (d, *J* = 6.5 Hz, 2H, $OC\underline{H_2}CH$), 3.64 (t, *J* = 7.3 Hz, 2H, $OC\underline{H_2}CH_2$), 2.91 (t, *J* = 7.3 Hz, 2H, $CH_2C\underline{H_2}Ph$), 2.44 – 2.24 (m, 1H, cyclohexyl CH), 1.97 – 1.84 (m, 1H, cyclohexyl CH'), 1.83 – 1.06 (m, 20H, alkyl CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4 (C), 139.3 (C), 129.0 (CH), 128.5 (CH), 126.3 (CH), 119.2 (CH), 71.0 (CH_2), 67.2 (CH_2), 41.4 (CH), 40.8 (CH), 36.6 (CH_2), 34.9 (CH_2), 31.1 (CH_2), 27.3 (CH_2), 26.8 (CH_2), 26.4 (CH_2), 26.3 (CH_2). Found (APCI) $[M+H]^+$ 327.2679, $C_{23}H_{35}O$ requires 327.2682.

(*E*)-(4-Phenethoxybut-2-en-2-yl)benzene **237p**:

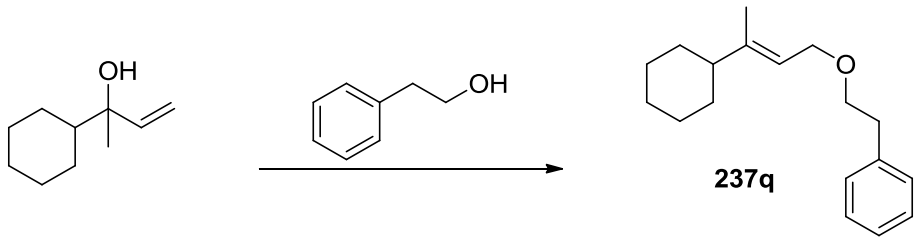


Analysis of crude reaction mixture showed that *E*:*Z* ratio was 6:1. Purified using flash column chromatography; using a gradient eluent system of neat hexane → 50:1 hexane:diethyl ether. Product obtained as a colourless oil with *E*:*Z* isomers present in 6:1 ratio (17.1 mg, 0.068 mmol, 67%). ν_{max}/cm^{-1} 3027 m 2919 m 2855 m (C-H), 1647 w (C=C), 1601 w 1495 m 1445 m (aromatic C=C), 1097 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.15 (m, 10H, aromatic CH), 5.94 (tq, *J* = 6.5, 1.2 Hz, 1H, $OCH_2C\underline{H}$), 4.22 (d, *J* = 6.5 Hz, 2H, $OC\underline{H_2}CH$), 3.72 (t, *J* = 7.3 Hz, 2H, $OC\underline{H_2}CH_2$), 2.95 (t, *J* = 7.3 Hz, 2H, $OCH_2C\underline{H_2}$), 2.07 (s, 3H, $CC\underline{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.0 (C), 139.1 (C), 138.3 (C), 129.1 (CH), 128.5 (CH), 128.3 (CH), 127.3 (CH), 126.3 (CH), 125.9 (CH), 124.5 (CH), 71.5 (CH_2), 68.1 (CH_2), 36.6 (CH_2), 16.3 (CH_3). Found (APCI) $[M+NH_4]^+$ 270.1851, $C_{18}H_{24}NO$ requires 270.1858.

2D NOESY confirms *E*-isomer is major isomer:

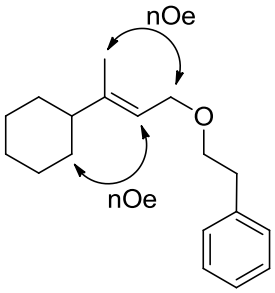


(*E*)-(2-((3-Cyclohexylbut-2-en-1-yl)oxy)ethyl)benzene **237q**:

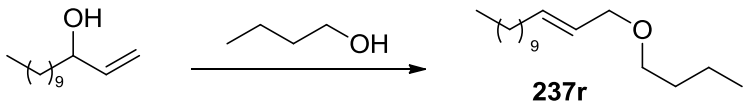


Analysis of crude reaction mixture showed that S_N2':S_N2 ratio was >20:1. The *E*:*Z* ratio was found to be ~5:1 Purified using flash column chromatography; using a gradient eluent system of neat hexane → 10:1 hexane:diethyl ether. Product obtained as a colourless oil with *E*:*Z* ratio of 5:1 (17.7 mg, 0.068 mmol, 71%). ν_{max}/cm^{-1} 3028 w 2923 s 2851 s (C-H), 1661 w (C=C), 1605 w 1496 m 1449 m (aromatic C=C), 1100 s (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.18 (m, 5H, aromatic CH), 5.33 (tp, *J* = 6.6, 1.1 Hz, 1H, $OCH_2C\underline{H}$), 4.03 (d, *J* = 6.5 Hz, 2H, $OC\underline{H_2}CH$), 3.64 (t, *J* = 7.4 Hz, 2H, $OC\underline{H_2}CH_2$), 2.91 (t, *J* = 7.4 Hz, 2H, $CH_2C\underline{H_2}Ph$), 1.91 – 1.64 (m, 5H, alkyl CH_2), 1.62 (app. s, 3H, $CH=C(C\underline{H_3})$), 1.36 – 1.09 (m, 5H, alkyl CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.2 (C), 139.2 (C), 129.0 (CH), 128.5 (CH), 126.3 (CH), 119.1 (CH), 71.2 (CH_2), 67.7 (CH_2), 47.3 (CH), 36.6 (CH_2), 31.7 (CH_2), 26.8 (CH_2), 26.5 (CH_2), 15.0 (CH_3). Found (APCI) $[M+NH_4]^+$ 276.2315, $C_{18}H_{30}NO$ requires 276.2322.

2D NOESY confirms *E*-isomer is major isomer:



(*E*)-1-Butoxypent-2-ene **237r**:

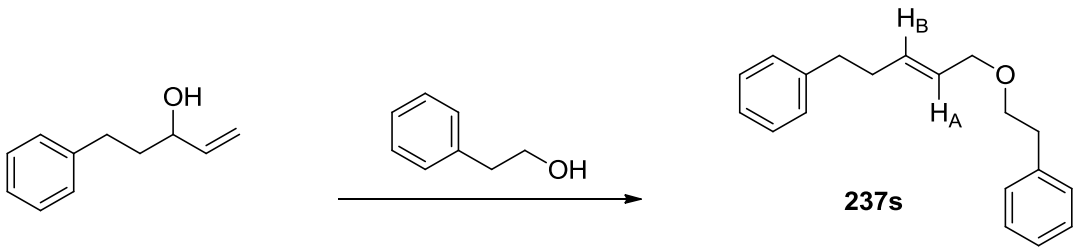


237r

To a 4 mL screw capped vial, tridec-1-en-3-ol (15.0 mg, 0.076 mmol) was added. n-Butanol (34.6 μL, 28.0 mg, 0.378 mmol) was added by microliter syringe. The solution was dissolved in 0.10 mL of toluene, and 2,6-di-*tert*-butylpyridine (1.2 mg, 0.0065 mmol) was added. To this solution, PPh_3AuNTf_2 (5.6 mg, 0.0076 mmol) was added, and washed in with 0.05 mL of toluene. The reaction was stirred at 40 °C for 65 hours, then was filtered through a plug of silica with diethyl ether and concentrated. Analysis of crude reaction mixture showed that *E*:*Z* ratio was 6:1, with S_N2':S_N2 ratio of 10:1. The product was purified using flash column chromatography with silver nitrate impregnated silica; using a gradient eluent system of neat petroleum ether → 100:1 petroleum ether:diethyl ether. Product obtained as a colourless oil in 6.3:1 *E*:*Z* ratio, with S_N2':S_N2 ratio of >20:1 (15.7 mg, 0.062 mmol, 82%).

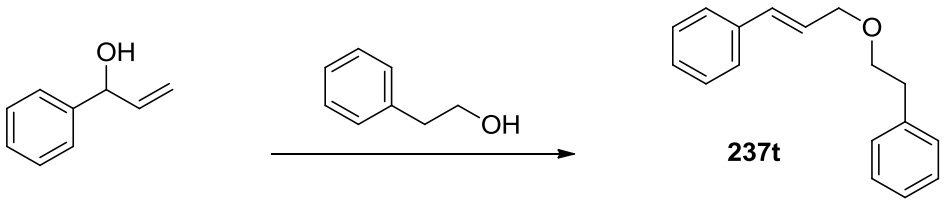
ν_{max}/cm^{-1} 2958 m 2924 s 2854 s (C-H), 1671 w (C=C), 1104 s (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 – 5.39 (m, 2H, C<u>H</u>=C<u>H</u>), 3.83 (d, *J* = 6.0 Hz, 2H, OC<u>H$_2$</u>CH), 3.33 (t, *J* = 6.7 Hz, 2H, OC<u>H$_2$</u>CH$_2$), 1.96 (q, *J* = 6.6 Hz, 2H, CHC<u>H$_2$</u>CH$_2$), 1.56 – 1.43 (m, 2H, OCH$_2$C<u>H$_2$</u>CH$_2$), 1.41 – 1.08 (m, 18H, alkyl CH_2), 0.85 (t, *J* = 7.3 Hz, 3H, CH$_2$C<u>H$_3$</u>), 0.81 (t, *J* = 6.7 Hz, 3H, CH$_2$C<u>H$_3$</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.7 (CH), 126.6 (CH), 71.8 (CH_2), 70.0 (CH_2), 32.5 (CH_2), 32.1 (CH_2), 32.0 (CH_2), 29.8 (CH_2 × 2), 29.7 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 22.9 (CH_2), 19.5 (CH_2), 14.3 (CH_3), 14.1 (CH_3). Found (EI) $[M]^+$ 254.2604, $C_{17}H_{34}O$ requires 254.2604.

(*E*)-(5-Phenethoxypent-3-en-1-yl)benzene **237s**:



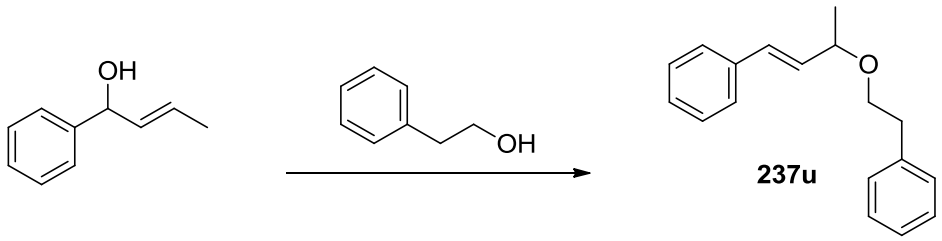
Analysis of crude ^{1}H NMR spectrum shows that *E*:*Z* ratio is 7:1, with S_N2':S_N2 ratio of 4.5:1 Purified using flash column chromatography; using a gradient eluent system of neat petroleum ether → 50:1 petroleum ether:diethyl ether. Product obtained as a colourless oil in 7:1 *E*:*Z* ratio (17.0 mg, 0.064 mmol, 69%). ν_{max}/cm^{-1} 3026 m 2922 m 2852 m (C-H), 1669 w (C=C), 1603 w 1496 m 1453 m (aromatic C=C), 1099 m (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.13 (m, 10H, aromatic CH), 5.73 (dtt, *J* = 15.3, 6.4, 1.0 Hz, 1H, CH_B), 5.59 (dtt, *J* = 15.3, 6.0, 1.0 Hz, 1H, CH_A), 3.94 (dq, *J* = 6.0, 1.0 Hz, 2H, $OC\underline{H_2}CH$), 3.61 (t, *J* = 7.4 Hz, 2H, $OC\underline{H_2}CH_2$), 2.90 (t, *J* = 7.4 Hz, 2H, $OCH_2C\underline{H_2}Ph$), 2.71 (t, *J* = 7.9 Hz, 2H, $CHCH_2C\underline{H_2}Ph$), 2.43 – 2.33 (m, 2H, $CH=CHC\underline{H_2}CH_2$).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.9 (C), 139.1 (C), 133.6 (CH), 129.0 (CH), 128.5 (CH), 128.5 (CH), 128.4 (CH), 127.1 (CH), 126.3 (CH), 126.0 (CH), 71.7 (CH_2), 71.1 (CH_2), 36.5 (CH_2), 35.6 (CH_2), 34.2 (CH_2). Found (ESI) $[M+NH_4]^+$ 284.2014, $C_{19}H_{26}NO$ requires 284.2009.

(*E*)-(2-(Cinnamyloxy)ethyl)benzene **237t**:[58]



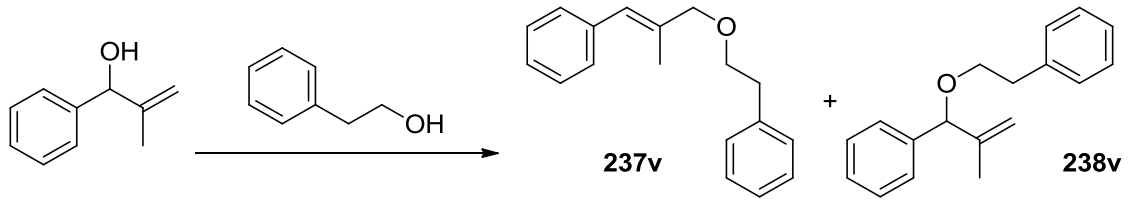
Analysis of crude ^{1}H NMR spectrum shows that *E*:*Z* ratio is 17:1. Purified using flash column chromatography; using an eluent system 80:1 petroleum ether:diethyl ether. Product obtained as a colourless oil (16.4 mg, 0.069 mmol, 61%). ν_{max}/cm^{-1} 3083 w 3063 w 3027 w 2924 w 2852 w (C-H), 1601 w (C=C), 1577 w 1495 m 1451 m (aromatic C=C), 1099 s 1080 s (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 6.96 (m, 10H, Ar-H), 6.51 (d, *J* = 16.0 Hz, 1H, Ph-C<u>H</u>=CH), 6.21 (dt, *J* = 16.0, 5.9 Hz, 1H, Ph-CH=C<u>H</u>), 4.10 (dd, *J* = 5.9, 1.4 Hz, 2H, CH=CH-C<u>H</u>$_2$), 3.64 (t, *J* = 7.2 Hz, 2H, $CH_2C\underline{H}_2O$), 2.87 (t, *J* = 7.2 Hz, 2H, Ph-C<u>H</u>$_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6 (C), 136.4 (C), 132.0 (CH), 128.7 (CH), 128.2 (CH), 128.1 (CH), 127.3 (CH), 126.2 (CH), 125.94 (CH), 125.85 (CH), 71.2 (CH_2), 71.0 (CH_2), 36.2 (CH_2).

(*E*)-(3-Phenethoxybut-1-en-1-yl)benzene **237u**:[59]



Analysis of crude ^{1}H NMR spectrum shows that S_N2':S_N2 ratio is 14:1. Purified using flash column chromatography; using a gradient eluent system of neat petroleum ether → 50:1 petroleum ether:diethyl ether. Product obtained as a colourless oil with *E*:*Z* ratio of >20:1 (9.5 mg, 0.038 mmol, 68%). ν_{max}/cm^{-1} 3026 m 2972 m 2926 m 2856 m (C-H), 1647 w (C=C), 1601 w 1495 m 1452 m (aromatic C=C), 1089 s (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.18 (m, 10H, aromatic CH), 6.48 (d, *J* = 16.0 Hz, 1H, CH=C<u>H</u>Ph), 6.10 (dd, *J* = 16.0, 7.5 Hz, 1H, CHC<u>H</u>=CH), 4.07 – 3.98 (m, 1H, OC<u>H</u>(CH_3)CH), 3.73 (ddd, *J* = 9.3, 8.0, 6.7 Hz, 1H, OC<u>H</u>H'CH_2), 3.58 (ddd, *J* = 9.3, 8.0, 6.7 Hz, 1H, OCH<u>H</u>'CH_2), 2.91 (t, *J* = 6.7 Hz, 2H, $CH_2C\underline{H_2}$Ph), 1.34 (d, *J* = 6.4 Hz, 3H, OCH(C<u>H</u>$_3$)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2 (C), 136.8 (C), 132.0 (CH), 131.1 (CH), 129.1 (CH), 128.7 (CH), 128.4 (CH), 127.7 (CH), 126.6 (CH), 126.3 (CH), 76.8 (CH), 69.6 (CH_2), 36.8 (CH_2), 21.8 (CH_3).

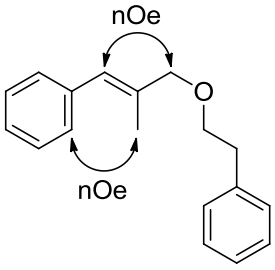
(*E*)-(2-Methyl-3-phenethoxyprop-1-en-1-yl)benzene **237v** + (2-methyl-1-phenethoxyallyl)benzene **238v**:



Analysis of crude ^{1}H NMR spectrum shows that S_N2':S_N2 ratio is 1:1. Purified using flash column chromatography; using a gradient eluent system of neat petroleum ether → 50:1 petroleum ether:diethyl ether. Product **237v** obtained as a colourless oil with *E*:*Z* ratio of >20:1 (9.5 mg, 0.038 mmol, 38%) and **238v** as a colourless oil (9.1 mg, 0.036 mmol, 36%).

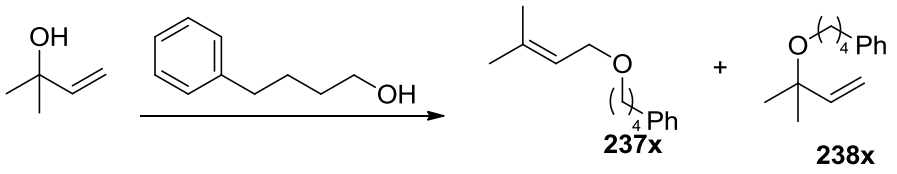
237v: ν_{max}/cm^{-1} 3025 m 2920 m 2854 m (C-H), 1659 w (C=C), 1600 m 1494 m 1453 m (aromatic C=C), 1095 s (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.12 (m, 10H, aromatic CH), 6.48 (s, 1H, C=C<u>H</u>Ph), 4.04 (d, *J* = 1.2 Hz, 2H, OC<u>H$_2$</u>C(CH$_3$)), 3.69 (t, *J* = 7.1 Hz, 2H, OC<u>H$_2$</u>CH$_2$), 2.95 (t, *J* = 7.1 Hz, 2H, CH$_2$C<u>H$_2$</u>Ph), 1.85 (d, *J* = 1.2 Hz, 3H, OCH$_2$C(C<u>H$_3$</u>)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2 (C), 137.7 (C), 135.4 (C), 129.10 (CH), 129.05 (CH), 128.5 (CH), 128.2 (CH), 126.8 (CH), 126.5 (CH), 126.3 (CH), 77.3 (CH_2), 71.1 (CH_2), 36.6 (CH_2), 15.5 (CH_3). Found (APCI) $[M]^+$ 252.1506, $C_{18}H_{20}O$ requires 252.1509.

2D NOESY confirms *E*-isomer is major isomer:



238v: ν_{max}/cm^{-1} 3027 m 2918 m 2857 m (C-H), 1650 w (C=C), 1602 w 1493 m 1451 m (aromatic C=C), 1096 s (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 – 7.13 (m, 10H, aromatic CH), 5.06 (dq, *J* = 1.5, 0.9 Hz, 1H, C=CH<u>H</u>), 4.90 (app. p, *J* = 1.5 Hz, 1H, C=C<u>H</u>H), 4.68 (s, 1H, OC<u>H</u>Ph), 3.68 – 3.48 (m, 2H, OC<u>H_2</u>CH_2), 2.91 (t, *J* = 7.1 Hz, 2H, OCH_2C<u>H_2</u>), 1.49 – 1.45 (m, 3H, $C(CH_2)C$<u>H_3</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.4 (C), 140.8 (C), 139.4 (C), 129.2 (CH), 128.4 (CH), 128.2 (CH), 127.4 (CH), 126.7 (CH), 126.2 (CH), 113.0 (CH_2), 85.5 (CH), 69.7 (CH_2), 36.6 (CH_2), 17.6 (CH_3). Found (APCI) $[M+H]^+$ 253.1585, $C_{18}H_{21}O$ requires 253.1587.

4-((3-Methylbut-2-en-1-yl)oxy)butyl)benzene **237x** + (4-((2-methylbut-3-en-2-yl)oxy)butyl)benzene **238x**:



Analysis of crude reaction mixture showed that S_N2':S_N2 ratio was 3.3:1. Purified using flash column chromatography; using a gradient eluent system of neat hexane → 50:1 hexane:diethyl ether. Product **237x** obtained as a colourless oil (26.2 mg, 0.120 mmol, 69%). Product **238x** obtained as a colourless oil (8.7 mg, 0.040 mmol, 23%)

237x: ν_{max}/cm^{-1} 3027 w 2932 m 2857 m (C-H), 1675 w (C=C), 1604 w, 1496 m 1452 m (aromatic C=C), 1087 s (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.19 (m, 5H, aromatic CH), 5.42 (tsept, *J* = 6.9, 1.4 Hz, 1H, $OCH_2C\underline{H}$), 4.00 (d, *J* = 6.9 Hz, 2H, $OC\underline{H_2}CH$), 3.49 (t, *J* = 6.3 Hz, 2H, $OC\underline{H_2}CH_2$), 2.70 (t, *J* = 7.3 Hz, 2H, $CH_2C\underline{H_2}Ph$), 1.81 (s, 3H, $C\underline{H_3}/C\underline{H_{3'}}$), 1.80 – 1.64 (m, 7H, 2 × CH_2 & $CH_3/CH_{3'}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.6 (C), 136.9 (C), 128.6 (CH), 128.4 (CH), 125.8 (CH), 121.4 (CH), 70.2 (CH_2), 67.4 (CH_2), 35.9 (CH_2), 29.6 (CH_2), 28.3 (CH_2), 26.0 (CH_3), 18.1 (CH_3). Found (APCI) $[M+NH_4]^+$ 236.2010, $C_{15}H_{26}NO$ requires 236.2009.

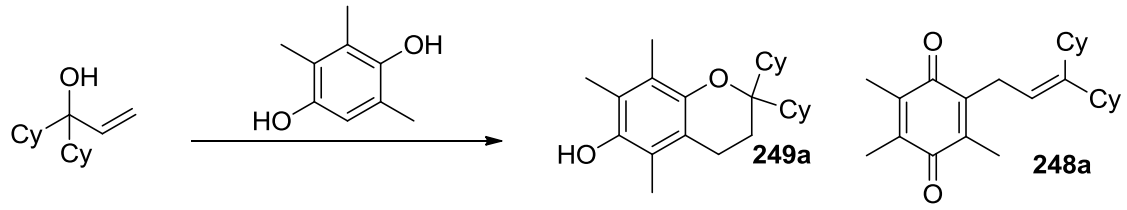
238x: ν_{max}/cm^{-1} 3027 w 2977 m 2932 m 2862 m (C-H), 1650 w (C=C), 1604 w 1496 m 1454 m (aromatic C=C), 1074 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.19 (m, 5H, aromatic CH), 5.89 (dd, *J* = 17.6, 10.8 Hz, 1H, $C\underline{H}=CH_2$), 5.24 – 5.13 (m, 2H, $CH=C\underline{H_2}$), 3.36 (t, *J* = 6.4 Hz, 2H, $OC\underline{H_2}CH_2$), 2.73 – 2.64 (t, *J* = 7.5 Hz, 2H, $CH_2C\underline{H_2}Ph$), 1.89 – 1.56 (m, 4H, alkyl CH_2), 1.33 (s, 6H, $C(C\underline{H_3})_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4 (CH), 142.8 (C), 128.6 (CH), 128.4 (CH), 125.8 (CH), 113.6 (CH_2), 74.9 (C), 62.5 (CH_2), 36.0 (CH_2), 30.3 (CH_2), 28.4 (CH_2), 26.0 (CH_3). Found (APCI) $[M+H]^+$ 219.1743, $C_{15}H_{23}O$ requires 219.1743.

General Synthetic Procedure for Allylic Etherification using (Trz)AuCl Complexes:

The gold(I) catalyst (0.0058 mmol, 5 mol%) was added to a solution of allylic alcohol **235c** (15 mg, 0.117 mmol) and 4-phenylbutanol **239** (19.6 μL, 19.3 mg, 0.129 mmol, 1.1 equiv.) in CH_2Cl_2 (0.1 mL). In a separate vial, silver hexafluoroantimonate (2.0 mg, 0.0058 mmol, 5 mol%) was dissolved in CH_2Cl_2 (0.1 mL), then transferred to the reaction mixture and washed in with CH_2Cl_2 (0.1 mL). The reaction was allowed to stir for 18 h at 25 °C. The crude mixture was filtered through a silica plug with diethyl ether, and concentrated under reduced pressure. The product **237e** was obtained as a colorless oil after purification by flash column chromatography (silica, gradient: neat hexane → 50:1 hexane:diethyl ether). Spectroscopic analyses were in agreement with those previously reported in literature.

2,2-Dicyclohexyl-5,7,8-trimethylchroman-6-ol **249a** &

2-(3,3-dicyclohexylallyl)-3,5,6-trimethylcyclohexa-2,5-diene-1,4-dione **248a**:



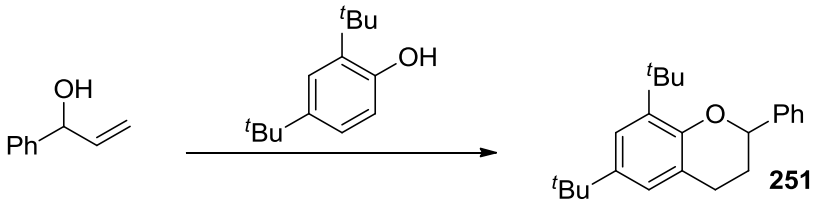
249a: Reaction carried out in a sealed tube. 1,1-Dicylohexylprop-2-en-1-ol **235e** (15.4 mg, 69.2 µmol) and trimethylhydroquinone (51.2 mg, 336 µmol) were dissolved in dioxane (0.14 mL). PPh_3AuNTf_2 (as a 2:1 toluene adduct) (2.7 mg, 3.7 µmol) was added to the resulting solution. The reaction was tightly sealed and allowed to stir at 90 °C for 65.5 hours. The reaction was then filtered over a plug of silica, using ethyl acetate as eluent. The crude mixture was purified using column chromatography, using a gradient eluent system of neat hexane to 20:1 hexane:ethyl acetate. Product **249a** was obtained as a brown oil (20.5 mg, 57.5 µmol, 83%).

ν_{max}/cm^{-1} 3465, 2923, 2852, 1449, 1420, 1260, 1213, 1082, 1067, 908, 733. ^1H NMR (300 MHz, $CDCl_3$) δ 4.15 (s, 1H, O<u>H</u>), 2.54 (t, *J* = 6.8 Hz, 2H, C<u>H</u>$_2$), 2.16 (s, 3H, C<u>H</u>$_3$), 2.11 (s, 6H, C<u>H</u>$_3$), 1.85 (t, *J* = 6.8 Hz, 2H, C<u>H</u>$_2$), 1.90 – 1.53 (m, 12H, Cy-<u>H</u>), 1.23 – 1.06 (m, 10H, Cy-<u>H</u>). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.9 (C), 144.3 (C), 122.6 (C), 121.1 (C), 118.3 (C), 117.9 (C), 80.1 (C), 43.8 (CH), 28.4 (CH_2), 28.0 (CH_2), 27.6 (CH_2), 27.2 (CH_2), 27.0 (CH_2), 23.4 (CH_2), 20.5 (CH_2), 12.4 (CH_3), 12.0 (CH_3), 11.4 (CH_3). Found (NSI+) $[M+H]^+$ 357.2788, $C_{24}H_{37}O_2$ requires 357.2788.

248a: 1,1-Dicylohexylprop-2-en-1-ol **235e** (15.1 mg, 67.9 µmol) and trimethylhydroquinone (51.0 mg, 335 µmol) were dissolved in dioxane (0.14 mL). PPh_3AuNTf_2 (as a 2:1 toluene adduct) (2.5 mg, 3.4 µmol) was added to the resulting solution. The reaction was sealed and allowed to stir at 80 °C for 65.5 hours. The reaction was then filtered over a plug of silica, using ethyl acetate as eluent. The crude mixture was purified using column chromatography, using a gradient eluent system of neat hexane to 7:1 hexane:ethyl acetate. Product **248a** was obtained as a yellow oil (8.5 mg, 24.0 µmol, 35%). (The major product is chroman **249a** at 45%)

ν_{max}/cm^{-1} 2924, 2851, 1642, 1448, 1374, 1302, 1262. ^1H NMR (300 MHz, $CDCl_3$) δ 4.88 (t, *J* = 6.9 Hz, 1H, C<u>H</u>), 3.25 (d, *J* = 6.9 Hz, 2H, C<u>H</u>$_2$), 2.63 – 2.48 (m, 1H, Cy-<u>H</u>), 2.05 – 1.96 (m, 9H, 3 × C<u>H</u>$_3$), 1.92 – 0.97 (m, 21H, Cy-<u>H</u>). ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.2 (C), 187.1 (C), 152.0 (C), 144.0 (C), 140.6 (C), 140.4 (C), 122.1 (C), 117.5 (CH), 41.1 (CH), 40.1 (CH), 35.2 (CH_2), 30.9 (CH_2), 27.3 (CH_2), 26.8 (CH_2), 26.4 (CH_2), 26.3 (CH_2), 24.9 (CH_2), 12.6 (CH_3), 12.5 (CH_3), 12.3 (CH_3). Found (NSI+) $[M+H]^+$ 355.2630, $C_{24}H_{35}O_2$ requires 355.2632.

6,8-Di-*tert*-butyl-2-phenylchroman **251**:



1-Phenylprop-2-en-1-ol **235i** (15.1 mg, 112.5 µmol) and 2,4-di-*tert*-butylphenol (115.4 mg, 559 µmol) were dissolved in toluene (0.10 mL). PPh_3AuNTf_2 (as a 2:1 toluene adduct) (4.1 mg, 5.5 µmol) was added to the resulting solution. $HNTf_2$ (1.6 mg, 5.7 µmol) was measured out in a glove box, then dissolved in toluene (0.13 mL), and added to the reaction vial. The reaction was allowed to stir at 60 °C for 41 hours. The reaction was then filtered through a plug of silica, using diethyl ether as the eluent. The crude mixture was purified using column chromatography, using neat hexane. The isolated material was impure, so a plug of silica was used to further purify the product. The impurity was washed off in neat hexane, and the desired product was obtained after an ether wash. Product **251** was obtained as a colourless oil (18.7 mg, 58.0 µmol, 52%).

ν_{max}/cm^{-1} 2952, 2867, 1496, 1476, 1444, 1361, 1231, 1127, 877, 752, 697. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.27 (m, 5H, C($C_6\underline{H}_5$)), 7.20 (d, *J* = 2.5 Hz, 1H, Ar-H), 6.98 (d, *J* = 2.4 Hz, 1H, Ar-H), 5.02 (dd, *J* = 10.5, 2.4 Hz, 1H, OCH), 3.08 (ddd, *J* = 16.5, 11.8, 6.5 Hz, 1H, CCH$\underline{H}$HCH$_2$), 2.85 (ddd, *J* = 16.5, 5.5, 2.6 Hz, 1H, CCH$\underline{H}$CH$_2$), 2.26 – 1.98 (m, 2H, CHC$\underline{H}_2$CH$_2$), 1.40 (s, 9H, C(C$\underline{H}_3$)$_3$), 1.32 (s, 9H, C(C$\underline{H}_3$)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.8 (C), 142.6 (C), 142.1 (C), 137.2 (C), 128.5 (CH), 127.7 (CH), 126.1 (CH), 124.4 (CH), 122.0 (CH), 121.2 (C), 77.9 (CH), 35.2 (C), 34.4 (C), 31.8 (CH_3), 30.8 (CH_2), 30.1 (CH_3), 26.4 (CH_2). Found (APCI) $[M-H]^+$ 321.2214, $C_{23}H_{29}O$ requires 321.2213.

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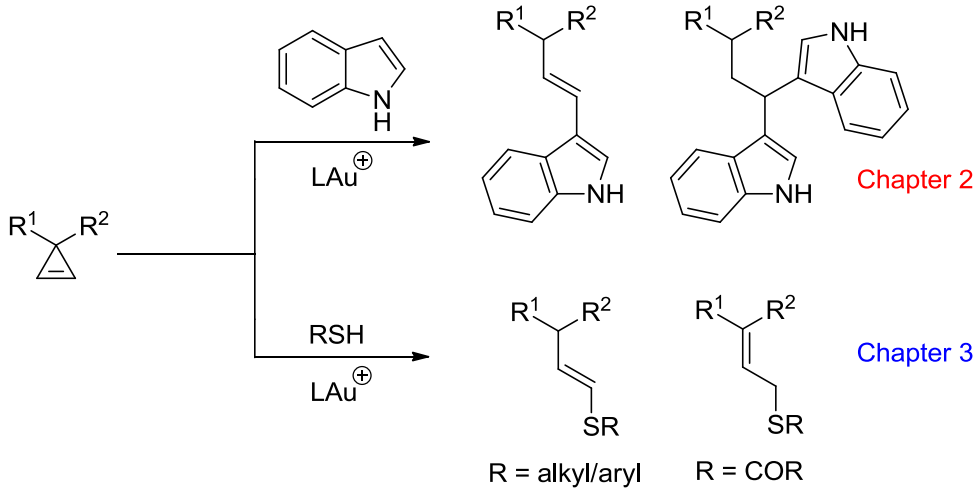
Chapter 6 – Conclusions

The area of homogeneous gold(I)-catalysis has expanded dramatically over the last 15 years, allowing a diverse range of reactions to be utilised in the synthesis of natural products and pharmaceutical agents. The work highlighted throughout this thesis has demonstrated how the power of gold(I)-catalysis can be harnessed to *control* reactions.

The gold(I)-catalysed addition of indole to cyclopropenes can be controlled to give either 3-(*E*)-vinylindoles, or *bis*-indolylalkanes (Chapter 2). The presence of bulky substituents on the cyclopropene substrate leads to unexpected oxidation products: *bis*-indolylalkenes and epoxides. These interesting oxidation products could provide an insight into further development of gold(I)-catalysed reactions, which include an oxidation step.

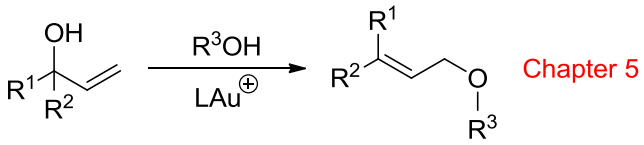
Thiols and thioacids were found to be viable nucleophiles in the gold(I)-catalysed addition to cyclopropenes (Chapter 3). The reaction could, once again, be controlled to achieve vinyl thioethers from thiol addition, or allylic thioesters from thioacids. The chemoselectivity of the reaction highlighted how the *S*-nucleophile affects the gold(I) catalyst.



Scheme 6.1 Gold(I)-catalysed additions of nucleophiles to cyclopropenes.

Gold(I) catalysts were found to form deactivated species, on addition of sulfur and nitrogen nucleophiles (Chapter 4). These complexes were found to form in competition with the desired reaction, and their formation provides a reason for the low reactivity of these nucleophiles in some gold(I) catalysed reactions.

The first intermolecular gold(I)-catalysed allylic etherification was also described, starting from allylic alcohol substrates and alcohol nucleophiles (Chapter 5). The generality of the reaction is excellent, and conditions were further improved with the use of novel 1,2,3-triazol-5-ylidene gold(I) catalysts. The future of this area looks promising, with the potential for chiral transfer reaction to be developed. Looking further into the future, the use of chiral catalysts may also lead to the development of catalytic enantioselective examples of this reaction.



Scheme 6.2. Gold(I)-catalysed allylic etherification.

Appendix – List of Publications

"Divergent Outcomes of Gold(I)-Catalyzed Indole Additions to 3,3-Disubstituted Cyclopropenes", P. C. Young, M. S. Hadfield, L. Arrowsmith, K. M. Macleod, R. J. Mudd, J. A. Jordan-Hore and A.-L. Lee, *Organic Letters*, 2012, **14**, 898-901.

"Gold(I)-Catalyzed Addition of Thiols and Thioacids to 3,3-Disubstituted Cyclopropenes", R. J. Mudd, P. C. Young, J. A. Jordan-Hore, G. M. Rosair and A.-L. Lee, *The Journal of Organic Chemistry*, 2012, **77**, 7633-7639.

"Gold(I)-catalysed direct allylic etherification of unactivated alcohols", P. C. Young, N. A. Schopf and A.-L. Lee, *Chemical Communications*, 2013, **49**, 4262-4264.

"Deactivation of Gold(I) Catalysts in the Presence of Thiols and Amines – Characterisation and Catalysis", P. C. Young, S. L. J. Green, G. M. Rosair and A.-L. Lee, *Dalton Transactions*, 2013, **42**, 9645-9653.

"Gold(I)-Catalysed One-Pot Synthesis of Chromans using Allylic Alcohols and Phenols", E. Coutant, P. C. Young, G. Barker and A.-L. Lee, *Beilstein Journal of Organic Chemistry*, 2013, **9**, 1797-1806.

"Gold(I) and Palladium(II) Complexes of 1,3,4-Trisubstituted 1,2,3-Triazo-5-ylidene Click Carbenes: Systematic Study of the Electronic and Steric Influence on Catalytic Activity", J. R. Wright, P. C. Young, N. T. Lucas, A.-L. Lee and J. D. Crowley, *Organometallics*, 2013, **32**, 7065-7076.